Montana Formulary Committee Clinical Class Reviews

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Drug Class:	Inhaled Corticosteroids				
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Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently five inhaled corticosteroids available in the United States as indicated above.
- All of the inhaled steroids are FDA approved for maintenance and prophylactic treatment of asthma.

Formulation

- There are two major delivery devices, the dry powdered inhaler (DPI) and the metered dose inhaler (MDI). The MDI requires appropriate technique to deliver the drug to lung tissues or use of a spacer device. The dry powder inhalers are free of additives and propellants, but the dry powder may act as an irritant.
- The DPI system is breath activated and may be easier to use since less coordination is needed. This ease of use may reduce systemic absorption. Currently fluticasone and budesonide have DPI delivery systems.

Potency

- The relative anti-inflammatory potency of inhaled corticosteroids are in the following order: flunisolide = triamcinolone acetonide < beclomethasone diproprionate= budesonide < fluticasone.
- Because of the possibility of higher systemic absorption, monitor patients using flunisolide for any evidence of systemic corticosteroid effect.
- The principle advantage of more potent inhaled corticosteroids may be in improved patient compliance and acceptance (less puffs per day) for those patients requiring higher dosages.

Efficacy

- Current data only supports a difference in potency, not efficacy, among the inhaled corticosteroids; thus when used in equipotent dosages, efficacy is equal among all agents.

Adverse Events

- Contraindications, warnings, adverse drug events, and drug interactions are similar for all inhaled steroids and are considered class effects. Refer to *Class Effects* table for more details.

Summary of Indications

Maintenance and prophylactic treatment of asthma; includes patients who require systemic corticosteroids and may benefit from systemic dose reduction/elimination.

Place in Therapy

From ERP-2:
"Inhaled corticosteroids are the most effective long-term therapy available for mild, moderate, or severe persistent asthma. In general, inhaled corticosteroids are well tolerated and safe at the recommended dosages. The potential but small risk of adverse events from the use of inhaled corticosteroids is well balanced by their efficacy".

Early intervention with inhaled corticosteroids can improve asthma control and normalize lung function and may prevent irreversible airway injury.

To reduce the potential for adverse effects, the following measures are recommended:

- Administer inhaled corticosteroids with spacers/holding chambers.
- Advise patients to rinse their mouths (rinse and spit) following inhalation.
- Use the lowest possible dose of inhaled corticosteroid to maintain control.
- To maintain control of asthma (especially for nocturnal symptoms), consider adding a long-acting inhaled beta2-agonist to a low-to-medium dose of inhaled corticosteroid rather than using a higher dose of inhaled corticosteroid.

Department of Veterans Affairs Formulary

FLUNISOLIDE ORAL INHALER

Summary of Pipeline Agents Expected to Offer Related Treatment Options

- Cicesonide is a pro-drug which is converted in the lower airways into an active metabolite which appears to bind avidly to corticosteroid receptors in the lower airways. Any cicesonide that is absorbed systemically is almost completely bound to plasma proteins, and thus is not in the free form capable of binding to receptors on systemic tissues. The cicesonide is then disposed of relatively rapidly in the liver. Thus, there is much less potential for systemic adverse effects of inhaled cicesonide.
- Cicesonide is formulated in a solution form with an HFA propellant that may allow for greater penetration than budesonide (which is in a particulate suspension).
- Once daily dosing.
- The manufacturer is seeking an indication for the treatment of persistent asthma (regardless of severity) in adults, adolescents and children four (4) years of age or older.

Class Effects:	Inhaled Corticosteroids
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Inhaled corticosteroids have anti-inflammatory effects of the bronchial mucosa of asthma patients. Treatment with inhaled corticosteroids for 1 to 3 months results in a reduction in mast cells, macrophages, T-lymphocytes, and eosinophils in the epithelium and submucosa in the bronchioles. By reducing airway inflammation, inhaled corticosteroids lessen airway hyperresponsiveness in asthmatic adults and children. Long-term therapy reduces airway responsiveness in asthmatic histamine cholinergic agonists, and allergens. Treatment also lowers responsiveness to exercise, fog, cold air, bradykinin, adenosine, and irritants. Inhaled corticosteroids make the airways less sensitive to these spasmogens and limit the maximal narrowing of the airway. Maximal effects of inhaled corticosteroid treatment may not be seen for several weeks.
Pediatric Labeling	Varies with product. See individual monographs.
Other studied uses	▪ Chronic obstructive pulmonary disease (COPD) ▪ Bronchopulmonary dysplasia (BPD) ▪ Cystic fibrosis ▪ Pulmonary sarcoidosis ▪ Prevention of post-bronchiolitis wheezing
Contraindications	▪ Hypersensitivity to any ingredients. ▪ The Rotadisk blisters containing fluticasone propionate inhalation powder (Flovent Rotadisk) also contain lactose, a milk protein. The list of adverse reactions observed during clinical practice was expanded to include anaphylactic reactions in patients with a severe allergy to milk protein.
Major AEs / Warnings	▪ Relief of acute bronchospasm; primary treatment of status asthmaticus or other acute episodes of asthma when intensive measures are required. ▪ Intranasal and inhaled corticosteroids may reduce growth in children; use the lowest effective dose; routinely monitor growth rate. ▪ Suppression of HPA function, hoarseness, dry mouth.
Pharmacokinetic issues	None

Drug Class:	Inhaled Corticosteroids				
Characteristic	**beclomethasone**	**budesonide**	**flunisolide**	**fluticasone**	**triamcinolone**
	Qvar®	Pulmicort Turbuhaler®, Pulmicort Respules®	AeroBid®, AeroBid-M®	Flovent®	Azmacort®
Date of FDA Approval	9/15/00	6/29/97-Turbohaler 8/8/00-Respules	8/17/84	3/27/96	4/23/82
Generic available?	No				
Manufacturer (if single source)	Ivax	Astra Zeneca	Forest	GlaxoSmithKline	Aventis
Dosage forms / route of admin	**HFA:** 40 mcg/actuation in 7.3 g canisters. 80 mcg/actuation in 7.3 g canisters. **Note:** Due to the smaller particle size of QVAR (an HFA product) the dose equivalent is ½ that of the former CFC beclomethasone products.	**Turbuhaler:** Powder: 200 mcg (each actuation delivers 160 mcg)/metered dose. **Respules**: Inhalation suspension for nebulization: 0.25 mg/2mL in single dose envelopes of 30. 0.5 mg/2mL in single dose envelopes of 30.	**AeroBid Aerosol:** 250 mcg/actuation. **AeroBid-M**: Menthol flavor: 250 mcg/actuation.	**Flovent: Aerosol** 44 mcg/actuation, 110 mcg/actuation, 220 mcg/actuation. **Flovent HFA**: Approved, but not yet available **Flovent Rotadisk Powder** – discontinued by manufacturer 8/2004 **Flovent Diskus Powder for inhalation:** FDA approved, but not marketed.	**Azmacort Aerosol** 100 mcg/actuation from spacer mouthpiece.

Drug Class:	Inhaled Corticosteroids				
Characteristic	**beclomethasone**	**budesonide**	**flunisolide**	**fluticasone**	**triamcinolone**
	Qvar®	Pulmicort Turbuhaler®, Pulmicort Respules®	AeroBid®, AeroBid-M®	Flovent®	Azmacort®
Number of Actuations (puffs or inhalations) per canister/Size of canister	HFA: Both strengths 100 actuations per 7.3g canister.	**Turbuhaler**: 200 doses per turbohaler. **Inhalation Suspension:** EDTA. In single-dose envelopes. (In 30s)	**Aerosol:** 100 metered doses per canister.	**Aerosol:** In 7.9 (institutional size) and 13g. canisters containing 60 and 120 metered doses respectively with propellants and with actuator. **HFA Aerosol:** In 12g canisters containing 120 metered doses	**Aerosol:** In 20 gm inhaler (60mg triamcinolone acetonide) with actuator (≥240 metered doses).
Dosing	BID Note: Due to the smaller particle size of QVAR (an HFA product) the dose equivalent is ½ that of the former CFC beclomethasone products.	BID – Turbuhaler QD-BID – Respules	BID	BID	TID-QID (may be given BID if double dose).

Drug Class:	Inhaled Corticosteroids				
Characteristic	**beclomethasone**	**budesonide**	**flunisolide**	**fluticasone**	**triamcinolone**
	Qvar®	Pulmicort Turbuhaler®, Pulmicort Respules®	AeroBid®, AeroBid-M®	Flovent®	Azmacort®
Pediatric Labeling	≥5 yo	▪ Pulmicort Turbuhaler: ▪ ≥6 years of age ▪ Pulmicort Respules: 12 months- 8 yo	≥6 yo	▪ Flovent Rotadisk: ≥4 years of age (discontinued by manf 8/2004) ▪ Flovent: ≥12 yo	≥6 yo
Drug interactions		▪ Ketoconazole inhibits CP4503A4, thus increasing plasma levels of budesonide. ▪ Clinical significance unknown due to low systemic absorption of Pulmicort.		▪ Ketoconazole inhibits CP4503A4, thus increasing plasma levels of fluticasone. ▪ Clinical significance unknown due to low systemic absorption of Flovent.	
Unique Features/Advantages	▪ HFA Inhaler ▪ Non CFC ▪ Smaller particle size allows for greater lung deposition (and thus efficacy of product).	▪ Breath actuated DPI Turbuhaler might be easier for small children and the elderly to co-ordinate. ▪ Only corticosteroid nebulizer available.	AeroBid-M has menthol flavoring.	Rotadisk is breath actuated.	Built in Spacer.

Drug Class:	Inhaled Corticosteroid/ß-Agonist Combination
Characteristic	fluticasone propionate and salmeterol
	Advair Diskus ®
Date of FDA Approval	August 24, 2000.
Generic available?	No
Manufacturer (if single source)	GSK
Dosage forms / route of admin	**Powder for inhalation**: 100 mcg fluticasone propionate, 50 mcg salmeterol 250 mcg fluticasone propionate, 50 mcg salmeterol 500 mcg fluticasone propionate, 50 mcg salmeterol
Number of Actuations (puffs or inhalations) per cannister/Size of canister	28 and 60 blisters in a disposable, purple-colored device.
Dosing	Adults and children 12 years of age: 1 inhalation twice daily (morning and evening, 12 hours apart). The maximum recommended dose of fluticasone propionate/salmeterol is 500 mcg/50 mcg twice daily.
FDA labeled indications	**Asthma, chronic:** ▪ For the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age. ▪ Not indicated for the relief of acute bronchospasm.
Other studied uses	COPD
Pediatric Labeling	= 12 years of age.
Contraindications	▪ Prior hypersensitivity to fluticasone or salmeterol ▪ Acute bronchospasm ▪ Status asthmaticus ▪ IgE-mediated allergic reactions to lactose or milk products
Major AEs / Warnings	Suppression of HPA function, hoarseness, dry mouth, reduction in growth velocity, tachycardia.

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Abstracts

Management of persistent symptoms in patients with asthma.

Lim KG.

Mayo Clin Proc. 2002 Dec;77(12):1333-8; quiz 1339.

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The main goals of asthma therapy are to control symptoms, prevent acute attacks, and maintain lung function as close to normal as possible. Customizing the regimen to relieve the patient's symptoms and control airway inflammation is important. If asthma is not well controlled, an initial inhaled corticosteroid boost will treat the underlying heightened airway inflammation, and the addition of a long-acting beta2-adrenergic agonist or leukotriene receptor antagonist will rapidly control symptoms. Most patients do not require prolonged treatment with expensive combination or additive agents.

Exercise-induced bronchoconstriction is a common source of symptoms. Treatments for scheduled and unscheduled exercises differ. Inhaled corticosteroids prevent frequent and severe asthma exacerbations. When patients have persistent symptoms despite a pharmacological regimen, environmental factors and nonpharmacological interventions must be considered before medication is increased. When an inhaled corticosteroid is being considered, issues of compliance, drug delivery device, and proper inhaler techniques are as important as issues of potency, clinical efficacy, and adverse effects. The new hydrofluoroalkane preparations offer more lung deposition and may be important in treating inflammation of the small airways in patients with asthma.

Establishing a therapeutic index for the inhaled corticosteroids: part I. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids.

Kelly HW.

J Allergy Clin Immunol. 1998 Oct;102(4 Pt 2):S36-51.

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The inhaled corticosteroids contain physicochemical differences that alter both glucocorticoid receptor-binding characteristics and the pharmacokinetic variables of these drugs. Differences in receptor-binding affinity translate into differences in potency for different drugs. Differences in pharmacokinetics, however, determine the topical effect to systemic effect ratio, or the "pulmonary targeting" of the drug. Beneficial pharmacokinetic properties that may improve pulmonary targeting include low oral bioavailability, rapid systemic clearance, and slow absorption from the lung.

Delivery devices can produce clinically significant differences in topical activity by altering the dose deposited in the lung and, for orally absorbed drugs, the amount deposited in the oropharynx and swallowed. Clinical trials have confirmed that differences in potency or drug delivery of 2-fold or more can be detected in patients with asthma. However, because of the relatively flat nature of the dose-response curve for morning peak expiratory flow and forced expiratory volume in 1 second, the trials must be adequately powered and well controlled.

The use of bronchial provocation measures are problematic because of the prolonged lag time for response. Study design flaws can lead to misinterpretation of results. Clinical studies have indicated the following relative potency differences: fluticasone propionate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide. Current evidence suggests that potency differences can be overcome by giving larger doses of the less potent drug. However, because of these potency differences, studies of systemic effects should not be done in isolation of adequate topical activity studies to define the pulmonary targeting of the drugs.

Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma.

Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ; EDICT Investigators.

Respir Med. 2002 Nov;96(11):851-61.

The aim of this study was to compare the efficacy safety and cost of Seretide (salmeterol/fluticasone propionate (Salm/FP), 50/250 microg bd) via Diskus with formoterol (Form; 12 microg bd) and budesonide (Bud; 800 microg bd) given concurrently (Form+Bud) via Turbuhaler in patients with moderate-to-severe asthma who were uncontrolled on existing corticosteroid therapy. The study used a randomised, double-blind, double-dummy, parallel-group design, consisting of a 2-week run-in period on current corticosteroid therapy (1000-1600 microg/day of BDP or equivalent) and a 12-week treatment period.

Symptomatic patients (n = 428) with FEV1 of 50-85% predicted and increased symptom scores or reliever use during run-in were randomly allocated to receive either Salm/FP (50/250 microg bd) via a single Diskus inhaleror Form+Bud (12+800 microg bd) via separate Turbuhalers. Clinic, diary card and asthma-related health-care resource utilisation data were collected.

Improvement in mean morning peak expiratory flow (PEFam was similar in the Salm/FP and Form+Bud groups. Both PEFam and mean evening PEF (PEFpm) increased by a clinically significant amount (>20 L/min) from baseline in both treatment groups. The mean rate of exacerbations (mild, moderate or severe) was significantly lower in the Salm/FP group (0.472) compared with the Form+Bud group (0.735) (ratio = 0.64; P < 0.001), despite the three-fold lower microgram inhaled corticosteroid dose in the Salm/FP group. Patients in the Salm/FP group also experienced significantly fewer nocturnal symptoms, with a higher median percentage of symptom-free nights (P = 0.04), nights with a symptom score <2 (P = 0.03), and nights with no awakenings (P = 0.02). Total asthma-related health-care costs were significantly lower in the Salm/FP group than the Form+Bud group (P<0.05). Both treatments were well tolerated, with a similar low incidence of adverse events.

This study showed that in symptomatic patients with moderate-to-severe asthma, Salm/FP (50/250 microg bd), administered in a single convenient device (Diskus), was at least as effective as an approximately three-fold higher microgram corticosteroid dose of Bud (800 microg bd) given concurrently with Form (12 microg bd) in terms of improvement in PEFam, and superior at reducing exacerbations and nights with symptoms or night-time awakenings. Salm/FP was also the less costly treatment due primarily to lower hospitalization and drug costs.

Comparison of inhaled corticosteroids.

Kelly HW.

Ann Pharmacother. 1998 Feb;32(2):220-32.

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OBJECTIVE: To review the comparative studies evaluating both efficacy and safety of inhaled corticosteroids in the management of asthma. Specifically, comparative clinical trials are evaluated that allow clinicians to determine relative potencies of the various inhaled corticosteroids.

METHODS: A critical review was performed of the published clinical trials, either as articles or abstracts, comparing the clinical efficacy or systemic activity of inhaled corticosteroids. No a priori criteria were applied, as this was not a meta-analysis.

FINDINGS: In vitro measures of antiinflammatory activity of corticosteroids consistently demonstrate potency differences among the various corticosteroids. Traditionally, these in vitro measures have been used to develop new corticosteroids with greater topical activity. While no accepted direct measure of antiasthmatic antiinflammatory activity exists, clinical trials using surrogate measures (e.g., forced expiratory volume in 1 second, peak expiratory flow, bronchial hyperresponsiveness, symptom control) indicate that in vitro measures provide a relatively accurate assessment of antiasthmatic potency. The relative antiinflammatory potency of the inhaled corticosteroids is in the following rank order. flunisolide = triamcinolone acetonide < beclomethasone dipropionate = budesonide < fluticasone. Studies of systemic activity appear to confirm this relative order of potency. Currently, no evidence exists for greater efficacy for any of the inhaled corticosteroids when administered in their relative equipotent dosages. The preponderance of current data suggests that when administered in equipotent antiinflammatory doses as a metered-dose inhaler plus spacer or as their respective dry-powder inhaler, the existing inhaled corticosteroids have similar risks of producing systemic effects.

CONCLUSIONS: Delivery systems can significantly affect both topical and systemic activity of inhaled corticosteroids. More direct comparative studies between agents are required to firmly establish comparative topical to systemic activity ratios. The preponderance of evidence suggests that the agents are not equipotent on a microgram basis.

Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD.

Cazzola M, Santus P, Di Marco F, Boveri B, Castagna F, Carlucci P, Matera MG, Centanni S.

Respir Med. 2003 May;97(5):453-7.

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In the present trial, we compared the broncholytic efficacy of the combination therapy with 50 microg salmeterol + 250 microg fluticasone and 12 microg formoterol + 400 microg budesonide, both in a single inhaler device, in 16 patients with moderate-to-severe COPD. The study was performed using a single-blind crossover randomized study. Lung function, pulse oximetry (SpO2) and heart rate were monitored before and 15, 30, 60, 120, 180, 240, 300, 360, 480, 600, and 720 min after bronchodilator inhalation.

Both combinations were effective in reducing airflow obstruction. FEV1 AUC(0-12 h) was 2.83 l (95% CI: 2.13-3.54) after salmeterol/fluticasone and 2.57 l (95% CI: 1.97-3.2) after formoterol/budesonide. Formoterol/budesonide elicited the mean maximum improvement in FEV1 above baseline after 120 min (0.29 l; 95% CI: 0.21-0.37) and salmeterol/fluticasone after 300 min (0.32 l; 95% CI: 0.23-0.41). At 720 min, the increase in FEV1 over baseline values was 0.10 l (95% CI: 0.07-0.12) after salmeterol/fluticasone and 0.10 l (95% CI: 0.07-0.13) after formoterol/budesonide. The mean peak increase in heart rate occurred 300 min after formoterol/budesonide (1.5 b/min; 95% CI--2.3 to 5.3) and 360 min after salmeterol/fluticasone (2.6 b/min; 95% CI--1.9 to 7.0). SpO2 did not change.

All differences between salmeterol/fluticasone and formoterol/budesonide were not significant ($P > 0.05$) except those in FEV1 at 120 and 360 min. The results indicate that an inhaled combination therapy with a long-acting beta2-agonist and an inhaled corticosteroid appears to be effective in improving airway limitation after acute administration in patients suffering from COPD.

Adding formoterol to budesonide in moderate asthma--health economic results from the FACET study.

Andersson F, Stahl E, Barnes PJ, Lofdahl CG, O'Byrne PM, Pauwels RA, Postma DS, Tattersfield AE, Ullman A; Formoterol and Corticosteroid Establishing Therapy. International Study Group.

Respir Med. 2001 Jun;95(6):505-12.

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The FACET (Formoterol and Corticosteroid Establishing Therapy) study established that there is a clear clinical benefit in adding formoterol to budesonide therapy in patients who have persistent symptoms of asthma despite treatment with low to moderate doses of an inhaled corticosteroid. We combined the clinical results from the FACET study with an expert survey on average resource use in connection with mild and severe asthma exacerbations in the U.K., Sweden and Spain.

The primary objective of this study was to assess the health economics of adding the inhaled long-acting beta2-agonist formoterol to the inhaled corticosteroid budesonide in the treatment of asthma. The extra costs of adding the inhaled beta2-agonist formoterol to the corticosteroid budesonide in asthmatic patients in Sweden were offset by savings from reduced use of resources for exacerbations. For Spain the picture was mixed. Adding formoterol to low dose budesonide generated savings, whereas for moderate doses of budesonide about 75% of the extra formoterol costs could be recouped. In the U.K., other savings offset about half of the extra cost of formoterol.

All cost-effectiveness ratios are within accepted cost-effectiveness ranges reported from previous studies. If productivity losses were included, there were net savings in all three countries, ranging from Euro 267-1183 per patient per year. In conclusion, adding the inhaled, long-acting beta2-agonist formoterol to low-moderate doses of the inhaled corticosteroid budesonide generated significant gains in all outcome measures with partial or complete offset of costs. Adding formoterol to budesonide can thus be considered to be cost-effective.

Drug Class:	Intranasal Steroids		
Drugs Reviewed:	flunisolide (Nasalide® & Nasarel®)	beclomethasone (Beconase AQ®, Vancenase AQ®,)	budesonide (Rhinocort Aqua®)
	fluticasone (Flonase®)	triamcinolone (Nasacort HFA ®, Nasacort AQ®)	mometasone (Nasonex®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently six intranasal steroids available in the United States as indicated above.
- All of the intranasal steroids are FDA approved for treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Half have an indication for the treatment of non-allergic perennial rhinitis, and one has an indication for prevention of recurrence of nasal polyps following surgical removal. (see *Summary of Indications* table that follows)
- Contraindications, warnings, adverse drug events, and drug interactions are similar for all intranasal steroids and are considered class effects. Refer to *Class Effects* table for more details.
- All intranasal steroids are available as sprays; triamcinolone (Nasacort® HFA) is available as an aerosol.
- The goal of continued research into inhaled glucocorticoids has been to minimize their oral bioavailability, to prolong their effect in the target organ and to improve their risk/benefit ratio. Clinical trials, to date, have shown equal efficacy and tolerability between the various agents.

Summary of Indications

Indication	flunisolide	beclomethasone	budesonide	fluticasone	triamcinolone	mometasone
	Nasalid® & Nasarel®	Beconase® AQ Vancenase AQ	Rhinocort®	*Flonase*®	*Nasacort HFA*®	*Nasonex*®
Seasonal allergic rhinitis (SAR)	✓	✓	✓	✓	✓	✓
Perennial allergic rhinitis (PAR)	✓	✓	✓	✓	✓	✓
Non-allergic perennial rhinitis	C	✓	✓[1]	✓	C	C
Prevention of recurrence of nasal polyps following surgical removal.		✓				

✓ = FDA approved indication C = Not FDA approved; however, studies indicate class effect

1. Adults only

Place in Therapy

Intranasal corticosteroids should be considered for first-line therapy of allergic rhinitis (Weiner et al, 1998; Nathan, 1996). Compared to antihistamines, decongestants, and mast cell stabilizers, intranasal corticosteroids have the following positive effects: (1) They suppress late phase allergic reactions and at least attenuate early phase reactions; (2) They are as effective as oral corticosteroids; (3) They reduce all nasal symptoms; and (4) They relieve upper airway inflammation which reduces seasonal asthma and decreases bronchial hyperreactivity.

Clinical studies have also shown that patients prefer intranasal corticosteroids over other treatments. Adverse reactions are usually limited to the nasal mucosa and are usually mild. Systemic adverse effects such as hypothalamic pituitary adrenal axis suppression and subcapsular lens changes are rare. Growth suppression in children has not been confirmed. Treatment with intranasal corticosteroids is also less expensive than other therapies.

Department of Veterans Affairs Formulary

"All of the available intranasal corticosteroids have been shown to be beneficial for the management of SAR and PAR. Furthermore, a review of the literature failed to demonstrate any clinically significant benefit of one agent over another with regard to efficacy. All agents are effective when administered once or twice daily and can be considered equally effective when used in equipotent doses. "

"In conclusion, the safety and efficacy of these agents in adult patients with SAR or PAR is similar. Therefore, the recommendation for choice of intranasal corticosteroid for the VA National Formulary should be based upon per patient cost. Furthermore, a contract should be sought for both an aerosol and an aqueous product, due to patient tolerability and preference for one mode of delivery over the other."

Summary of Pipeline Agents Expected to Offer Related Treatment Options

None

Class Effects:	Intranasal Steroids
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	These drugs have potent glucocorticoid activity and weak mineralocorticoid activity. The mechanisms responsible for the anti-inflammatory action of corticosteroids on the nasal mucosa are unknown. However, glucocorticoids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in allergic and nonallergic/irritant-mediated inflammation. These agents, when administered topically in recommended doses, exert direct local anti-inflammatory effects with minimal systemic effects. Exceeding the recommended dose may result in systemic effects, including hypothalamic-pituitary-adrenal (HPA) function suppression.
Pediatric Labeling	The safety and effectiveness have not been established in pediatric patients under six years of age, with the exceptions of fluticasone (Flonase®);<4 years and mometasone (Nasonex®); <2 years.
Other Studied Uses	Rhinosinusitis, Adjunctive treatment
Contraindications	Untreated local infections, hypersensitivity
Major AEs / Warnings	Local burning or stinging, throat irritation, bad taste, sneezing, itching, epitasis Watch for systemic effects
Drug Interactions	No significant drug interactions
Special Populations	
Hepatic Impairment	No adjustment needed
Pregnancy	Pregnancy Category C Rhinocort Aqua – Pregnancy Category B (rating changed 8/2004)
Geriatric	No adjustment needed
Race	No specific data available

Drug Class:	Intranasal Steroids			
Characteristic	*flunisolide*		*beclomethasone*	*budesonide*
	Nasalide® & generics	Nasarel®	Beconase® AQ, Vancenase AQ®	Rhinocort® Aqua
Date of FDA Approval[1]	Approved prior to Jan 1, 1982	March 08, 1995	July 27, 1987	February 14, 1994
Generic available? [1]	Yes	No	No	No
Manufacturer[1] (if single source)		Dura	Glaxo SmithKline/Schering	AstraZeneca
Dosage forms / route of administration	25 mcg/spray	29 mcg/spray	42 mcg/spray	32 mcg/spray or 64 mcg/spray (Each actuation of Rhinocort® nasal inhaler releases the equivalent of 50 µg of budesonide from the valve. However, only 32 µg is delivered from the nasal adapter. The manufacturer expresses the recommended dose based on amount delivered from the nasal adapter)
Dosing frequency	2-3 times daily		twice daily	once daily
General dosing guidelines [5,8-12]	**Adults:** Starting dose is 2 sprays (50 mcg) in each nostril 2 times a day (total dose 200mcg/day). May increase to 2 sprays in	**Adults:** Recommended starting dose is 2 sprays (58 mcg) in each nostril 2 times a day (total dose 232	**Adults and children 12 years of age:** Usual dosage is 1 or 2 inhalations (42mcg to 84mcg in each nostril twice a day (168 to 336 mcg/day).	**Adults and children 6 years of age and older:** 64 mcg/day administered as 1 spray/nostril once daily. Some patients who do not achieve symptom control

Drug Class:	Intranasal Steroids			
Characteristic	*flunisolide*		*beclomethasone*	*budesonide*
	Nasalide® & generics	Nasarel®	Beconase® AQ, Vancenase AQ®	Rhinocort® Aqua
	each nostril 3 times a day (total dose 300mcg/day). Maximum daily dose is 8 sprays in each nostril (400 mcg/day). **Children 6 to 14 years of age:** Starting dose is 1 spray (25 mcg) in each nostril 3 times a day or 2 sprays (50 mcg) in each nostril 2 times a day (total dose 150 to 200 mcg/day). Maximum daily dose is 4 sprays in each nostril (200 mcg/day). Improvement in symptoms usually becomes apparent within a few days. However, relief may not occur in some patients for as long as 2 weeks. Do not use > 3 weeks in absence of	mcg/day). The maximum total daily doses should not exceed 8 sprays in each nostril per day (464 mcg/day **Children 6 to 14 years of age:** Starting dose is 1 spray, (29 mcg) in each nostril 3 times a day (total dose 174 mcg/day) or 2 sprays (58 mcg) in each nostril 2 times a day (total dose 232 mcg/day). Maximum daily doses should not exceed 4 sprays in each nostril per day (total dose 232 mcg/day).	**Children 6 to 12 years of age:** Start with 1 inhalation in each nostril twice daily; patients not adequately responding to 168mcg or those with more severe symptoms may use 336 mcg (2 inhalations in each nostril). Once adequate control is achieved, the dosage should be decreased to 84 mcg (1 spray in each nostril) twice daily	at the recommended starting dose may benefit from an increased dose. Maximum recommended doses: **Adults 12 years of age and older:** mcg/day administered as 4 sprays/nostril once daily. **Children 6 through 11 years of age:** 128 mcg/day administered as 2 sprays/nostril once daily.

Drug Class:	Intranasal Steroids			
Characteristic	*flunisolide*		*beclomethasone*	*budesonide*
	Nasalide® & generics	Nasarel®	Beconase® AQ, Vancenase AQ®	Rhinocort® Aqua
	significant symptomatic improvement.			
FDA Labeled Indications[5,8,12-12]	SAR, PAR		▪ SAR, PAR ▪ Prevention of recurrence of nasal polyps following surgical removal. ▪ non-allergic (vasomotor) rhinitis (Vancenase AQ)	SAR, PAR
Pharmacokinetics issues (bioavailability) [5,8,12-12]	50%	Nasarel® and Nasalide® are not bioequivalent. Total absorption for Nasarel® was 25% less than Nasalide®.	≈20% (Theoretical estimate from inhaled beclomethasone)	≈10%, oral

Drug Class:	Intranasal Steroids		
Characteristic	***fluticasone***	***triamcinolone***	***mometasone***
	Flonase®	Nasacort AQ® Nasacort HFA®	Nasonex®
Date of FDA Approval[1]	October 19, 1994	Nasacort AQ® - May 20, 1996 Nasacort HFA® – May 7, 2004	October 1, 1997
Generic available? [1]	No	No	No
Manufacturer[1] (if single source)	Glaxo SmithKline	Aventis	Schering Plough
Dosage forms / route of admin	50 mcg/spray	55 mcg/spray	50 mcg/ spray
Dosing frequency	once daily - BID	once daily	once daily
General dosing guidelines [6,7,9]	**Adults:** Recommended starting dose is 2 sprays (50 mcg each) per nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 am and 8 pm) is also effective. Maximum total daily dosage should not exceed 200mcg/day (2 sprays per	**Adults and children 12 years of age and older:** The recommended starting and maximum dose is 220mcg/day as 2 sprays in each nostril once daily. When the maximum benefit has been achieved and symptoms have been controlled in patients initially controlled at 220mcg/day, decreasing the dose to 110mcg/day (1spray in each nostril per day) has been demonstrated to be effective in maintaining control of allergic	**Adults & children =12 years of age:** The recommended dose is 2 sprays (50 mcg/spray) in each nostril once daily (total daily dose, 200 mcg). In patients with a known seasonal allergy that precipitates nasal symptoms of seasonal allergic rhinitis, prophylaxis with mometasone (200mcg/day) is recommended 2 to 4 weeks prior to the anticipated start of the pollen

Drug Class:	Intranasal Steroids		
Characteristic	***fluticasone***	***triamcinolone***	***mometasone***
	Flonase®	Nasacort AQ® Nasacort HFA®	Nasonex®
	nostril). **Adolescents and children 4 years of age and older:** Start with 100 mcg (1 spray per nostril once a day). Patients not adequately responding to 100 mcg may use 200 mcg (2 sprays per nostril). Total daily dosage should not exceed 200 mcg/day.	rhinitis symptoms. **Children 6 through 11 years of age:** The recommended starting dose is 110 mcg/day given as 1 spray in each nostril once daily. The maximum recommended dose is 220 mcg/day as 2 sprays per nostril once daily. Once symptoms are controlled, pediatric patients may be maintained on 110 mcg/day (1 spray in each nostril per day).	season. **Children 2 to 11 years of age:** The recommended dose is 1 spray (50 mcg) in each nostril once daily (total daily dose, 100 mcg).
FDA Labeled Indications[6,7,9]	SAR, PAR Non-allergic perennial rhinitis	SAR, PAR	SAR, PAR
Pharmacokinetics issues [6,7,9] (bioavailability)	<2%, absolute	25% (Data from oral inhalation)	0.1%

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6. Product Information: Flonase(R), fluticasone propionate. GlaxoSmithKline, Research Triangle Park, NC, (PI revised 5/2003) reviewed 6/2003.
7. Product Information: Nasacort(R) nasal inhaler, triamcinolone acetonide. Rhone-Poulenc Rorer Pharmaceuticals, Inc, Collegeville, PA, reviewed 7/2004.
8. Product Information: Nasalide(R), flunisolide nasal solution. Dura Pharmaceuticals, Inc., San Diego, CA, USA, Reviewed 7/2004.
9. Product Information: Nasonex(R), mometasone furoate nasal spray. Schering Laboratories, Springfield, NJ, USA, reviewed 7/2004.
10. Product Information: Nasarel(R), flunisolide nasal solution. IVAX laboratories, Miami, FL, USA, reviewed 7/2004
11. Product Information: Rhinocort Aqua(TM), budesonide nasal spray . AstraZeneca LP, Wilmington, DE, reviewed 07/2003.
12. Product Information: Vancenase AQ(R), mometasone furoate nasal spray. Schering Corporation, Kenilworth, NJ, USA, reviewed 7/2004

Abstracts

Fluticasone vs. Beclomethasone: Fluticasone propionate 200 mcg intranasally once a day was compared to beclomethasone dipropionate 168 mcg intranasally twice a day for seasonal allergic rhinitis. A total of 313 patients were randomized to receive either treatment or placebo in a double-blind manner for 2 weeks. Although both treatments were significantly more effective than placebo in relieving symptoms of rhinitis, there was no difference between active treatments. Intranasal fluticasone once a day was as effective as beclomethasone twice a day for the topical treatment of allergic rhinitis.

Ratner P, Paull B, Findlay S et al: Fluticasone propionate given once daily is as effective as beclomethasone dipropionate given twice daily in relieving symptoms of seasonal allergic rhinitis (abstract). J Allergy Clin Immunol 1990; 85:163

Fluticasone vs Budesonide: Budesonide aqueous nasal spray and fluticasone aqueous nasal spray were effective for treating perennial allergic rhinitis (Day & Carrillo, 1998). Of the 273 patients enrolled, 111, 109, and 53 were randomized to 6 weeks of treatment with budesonide 256 micrograms (mcg) daily, fluticasone 200 mcg daily, and placebo spray, respectively. Double-blinding was used for budesonide and placebo; whereas, only the investigator was blinded for fluticasone. The reduction from baseline in combined nasal symptom scores was 2.11 (p less than 0.001) and 1.65 (p=0.0012) for budesonide and fluticasone, respectively; the difference between active treatments was also significant for combined nasal symptoms but not for individual symptom scores. No statistically significant difference in adverse effects was identified between active treatments and placebo. The newly reformulated budesonide nasal spray is effective and safe for treating perennial allergic rhinitis.

Day J & Carrillo T: Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol 1998; 102:902-908.

Mometasone vs. Beclomethasone: In a randomized, double-blind study of 427 patients with allergic rhinitis, one daily dose of MOMETASONE aqueous nasal spray was as effective as twice daily BECLOMETHASONE during a 3-month treatment period. All patients had positive skin reactions to at least one allergen, and the average perennial allergic rhinitis history was 11 years. Patients were allocated to receive either mometasone furoate 200 micrograms once daily (n=143), beclomethasone dipropionate 200 micrograms twice daily (n=146), or placebo (n=138). In a double-dummy design, mometasone-treated patients received two sprays of active treatment and two sprays of placebo each morning, along with two placebo sprays each evening. Beclomethasone patients received two sprays each of active drug and placebo both morning and evening. While both active treatments were statistically superior to placebo, there was no significant difference between mometasone and beclomethasone in symptom improvement. Adverse effects, most commonly epistaxis and headache, were similar among all three groups and were considered mild to moderate.

Drouin M, Yang WH, Bertrand B et al: Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol 1996; 77:153-160.

Montelukast vs. Budesonide: In patients with concomitant allergic rhinitis and asthma, oral montelukast and budesonide (inhaled plus nasal) were both better than placebo in relieving lower airway inflammation, but only budesonide improved upper respiratory parameters. Both treatments brought significant improvements in total seasonal allergic rhinitis symptoms and eye symptoms, but only budesonide improved nasal symptoms and daily activity scores. In a randomized, single-blind, placebo-controlled, double-dummy crossover study, 12 patients

were given inhaled budesonide 400 micrograms (mcg) and intranasal aqueous budesonide 200 mcg once daily for 2 weeks and oral montelukast 10 milligrams once daily for 2 weeks, with a 1- week run-in period before the initial treatment and a 1-week washout between the 2 treatments. Six patients started with budesonide and 6 with montelukast. There was much interindividual variation with montelukast, with some patients responding as well to montelukast as to budesonide and others having little response to montelukast compared with their response to budesonide (Wilson et al, 2001).

Wilson A, Dempsey OJ, Sims EJ et al: A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. Clin Exper Allergy 2001; 31:616-624.

Drug Class:	Leukotriene Modifiers	
Drugs Reviewed:	zafirlukast (Accolate®)	montelukast (Singulair®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently two leukotriene modifiers available in the United States as indicated above.
- There are currently two FDA approved indications for one or more of the leukotriene modifiers. (see *Indications Table* that follows)
- All of the leukotriene modifiers are FDA approved for treatment of asthma.
- Contraindications, warnings, and adverse drug events are similar for all leukotriene modifiers and are considered class effects. Refer to *Class Effects* table for more details. Drug interactions are different—refer to individual drug monographs.

Summary of Indications

- Both montelukast and zafirlukast have a FDA indication for prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older.
- Montelukast also has an indication for the relief of symptoms of seasonal allergic rhinitis in adults and children 2 years of age and older.

Place in Therapy

- Leukotriene modifiers are generally recommended as an alternative to inhaled steroids in patients with mild persistent asthma symptoms, and as add-on therapy in patients with moderate persistent asthma symptoms. British but not U.S. asthma guidelines support their use in patients with more severe asthma symptoms.
- This class is effective monotherapy for mild persistent asthma, however in comparison studies, neither agent in this class is as effective as an inhaled corticosteroid in improving lung function. Improvement in lung function was generally 12-15% for the inhaled corticosteroids and 5-8% for the leukotriene modifiers.
- Montelukast is indicated for the treatment of seasonal allergic rhinitis, although studies have shown that it is no more effective, or less effective, than antihistamines and nasal steroids.
- Leukotriene modifiers have shown some efficacy in exercise-induced asthma but should not be used as monotherapy for this condition. They have also been studied for the treatment of chronic urticaria.

Department of Veterans Affairs Formulary

Zafirlukast

Summary of Pipeline Agents Expected to Offer Related Treatment Options

- Selective phosphodiesterase 4 inhibitors

  Roflumilast: Roflumilast is an investigational oral phosphodiesterase type-4 inhibitor is being co-developed by Altana and Pfizer as a treatment for COPD and asthma. In Phase III trials, and filed for European approval 2/2004.

  The RECORD study was a 24-week, double blind, placebo-controlled trial that involved more than 1400 patients with moderate to severe COPD. The results of the study showed that patients who received roflumilast 250 or 500 mcg experienced significantly improved lung function vs. those taking placebo ($P = 0.0134$ and $P < 0.0001$, respectively) from baseline as measured by the amount of air exhaled in one second. On the other hand, patients who received placebo showed a significant decline in lung function from baseline ($P = 0.0041$). Similarly, the amount of air exhaled in six seconds (FEV_6) significantly improved in patients taking roflumilast 500 mcg vs. significant deterioration in patients who are taking placebo.

  Additionally, patients treated with roflumilast 500 mcg experienced 34% fewer exacerbations vs. those taking placebo. The mean number of exacerbations in the roflumilast treatment group was 1.03 and 0.75 for the 250 and 500 mcg, respectively vs. 1.13 for those taking placebo over the 24-week trial period ($p = 0.029$).

  Roflumilast was also generally well tolerated in the treatment of patients with COPD. Side effects due to study medication (250 or 500 mcg) included diarrhea (2.3%, 6.1%), nausea (1%, 3.2%), headache (0.7%, 1.8%) and stomach pain (0.2%, 1.6%). Most of the side effects were mild or moderate in severity and only less than 3% of patients who experienced these side effects discontinued the study.

- Anti-IgE monoclonal antibodies

Class Effects:	Leukotriene Modifiers
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	The sulfidopeptide leukotrienes—leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4)—are potent mediators of inflammation and appear to play a role in the pathogenesis of asthma. Previously referred to as slow-reacting substances of anaphylaxis, these compounds induce numerous pathophysiologic alterations, including increased airway reactivity, bronchoconstriction, and increased vascular permeability (resulting in mucosal edema). The most potent of these leukotrienes appears to be LTD4, which is 300 to 6000 times more potent than histamine or methacholine as a bronchoconstrictor. These data have led to development of leukotriene receptor antagonists for therapeutic use in asthma. Selective leukotriene receptor antagonists produce selective, competitive, reversible leukotriene D4 and E4 (LTD4 and LTE4) receptor antagonists. The leukotriene believed to mediate inflammation in COPD is LTB4 and in asthma is LTD4. Montelukast and zafirlukast do not inhibit the LTB4 receptor and therefore,are not expected to improve pulmonary function and symptoms of COPD[5].
Contraindications	Hypersensitivity
Major AEs / Warnings	▪ Should not be used for the reversal of acute asthma attacks. ▪ Eosinophilia – rare cases consistent with Churg-Strauss Syndrome. ▪ Use with caution in severe liver disease.
Key Populations	
Hepatic Impairment	Mild to moderate hepatic impairment increases AUC and slightly increases half-life – no dosing adjustment necessary.
Renal Impairment	Dosage does not need to be adjusted in patients with renal impairment.
Pregnancy	Category B
Lactation	▪ Zafirlukast is excreted in breast milk and should not be used in nursing women. ▪ It is not known if montelukast is excreted in breast milk. Use with caution in nursing women.
Geriatric	▪ Although specific dosage recommendations are not available, the clearance of zafirlukast is reduced in patients over the age of 65 years resulting in a peak concentration (Cmax) and area under the concentration-time curve (AUC) approximately twice those in younger adults. However, in clinical trials, this has not resulted in an increased incidence of adverse effects. ▪ Elderly patients, pediatric patients, male patients, female patients, and patients with renal insufficiency have similar montelukast plasma pharmacokinetic profiles as do young adult patients.
Race	▪ No data

Drug Class:	Leukotriene Modifiers	
Characteristic	**zafirlukast**	**montelukast**
	Accolate®	**Singulair®**
Date of FDA Approval	September 26, 1996	February 20, 1998
Generic available?	No	No
Manufacturer (if single source)	AstraZeneca	Merck
Dosage forms / route of administration	10 mg, 20 mg tablets for oral administration	10 mg tablets for oral administration 4mg, 5 mg chewable tablets 4 mg (packet) granules for oral administration (contents can be administered orally or mixed with soft foods – the contents should not be dissolved in liquids)
Dosing frequency	BID	QD
General dosing guidelines	Adults and children = 12 years of age - 20 mg bid Children 5-11 years of age – 10 mg bid	Adults and adolescents = 15 years of age – 10 mg qd Children 6 to 14 years of age – 5 mg qd Children 2 to 5 years of age – 4 mg qd Children 12 to 23 months with asthma – 4 mg qd
Pediatric Labeling	5 years and older	12 months and older
Adverse Events	Most common – headache, nausea, infection Less common - diarrhea, dizziness, ALT elevation, hypersensitivity reactions – including angioedema, urticaria, and rash	Most common – headache, abdominal pain, influenza, cough Less common - dyspepsia, dizziness, ALT/AST elevation, fatigue, rash Chewable tablets contain phenylalanine.
Drug Interactions	Aspirin, Erythromycin, Theophylline, Warfarin	Phenobarbital, Rifampin
Pharmacokinetic Issues	Take on an empty stomach - food decreases bioavailability by about 40%. Onset = 30 minutes Duration = 12 hours	Onset = 3-4 hours Duration = up to 24 hours

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Abstracts

Oral Montelukast Compared with Inhaled Salmeterol To Prevent Exercise-Induced Bronchoconstriction - A Randomized, Double-Blind Trial

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Background: Montelukast, an oral, once-daily leukotriene receptor antagonist, provides protection against exercise-induced bronchoconstriction.

Objective: To evaluate the effect of 8 weeks of therapy with salmeterol aerosol or montelukast on exercise-induced bronchoconstriction in adults with asthma.

Design: 8-week multicenter, randomized, double-blind study.

Setting: 17 asthma treatment centers in the United States.

Patients: 191 adults with asthma who had documented exercise-induced bronchoconstriction.

Intervention: Qualified patients were randomly assigned to double-blind treatment with montelukast (10 mg once in the evening) or salmeterol (50 µg [2 puffs] twice daily).

Measurements: Changes in pre-exercise and post-exercise challenge values; percentage inhibition in the maximal percentage decrease in FEV_1; the area above the FEV_1-time curve; and time to recovery of FEV_1 at days 1 to 3, week 4, and week 8 of treatment.

Results: By day 3, similar and statistically significant reductions in maximal percentage decrease in FEV_1 were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks 4 and 8; at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week 8, the percentage inhibition in the maximal percentage decrease in FEV_1 was 57.2% in the montelukast group and 33.0% in the salmeterol group (P = 0.002). By week 8, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV_1 of less than 20%.

Conclusions: The bronchoprotective effect of montelukast was maintained throughout 8 weeks of study. In contrast, significant loss of bronchoprotection at weeks 4 and 8 was seen with salmeterol. Long-term administration of montelukast provided consistent inhibition of exercise-induced bronchoconstriction at the end of the 8-week dosing interval without tolerance.

*For members of the Exercise Study Group, see the Appendix.

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Randomized Placebo-controlled Study Comparing a Leukotriene Receptor Antagonist and a Nasal Glucocorticoid in Seasonal Allergic Rhinitis

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Allergic rhinitis is an inflammatory disorder associated with local leukotriene release during periods of symptoms. Therefore, it has been suggested that antileukotrienes may be beneficial in the treatment of this disease. Leukotriene receptor antagonists have recently become available for asthma treatment, but little is known of their effects on allergic rhinitis. We have evaluated the effects of the leukotriene receptor antagonist zafirlukast versus placebo in patients with allergic rhinitis during the grass pollen season, using the nasal glucocorticoid beclomethasone dipropionate (BDP) as a positive treatment control. Thirty-three patients with seasonal allergic rhinitis were in a double-blind, double-dummy fashion randomized to treatments with oral zafirlukast (20 mg twice a day), intranasal beclomethasone dipropionate (200 μg twice a day), or placebo. The treatment was initiated 3 wk prior to the expected beginning of the grass pollen season. Patients completed a daily symptom-score list for sneezing, rhinorrhea, nasal itch, and nasal blockage during the 50-d treatment period. Nasal biopsies for quantification of local tissue eosinophilia (immunohistochemistry; EG2) were taken 1 mo before initiation of treatment and immediately after the peak of grass pollen season.

Patients receiving treatment with zafirlukast had degrees of nasal symptoms similar to those in the placebo group, whereas the BDP group had significantly less symptoms compared with both treatments ($p = 0.01$ and $p = 0.005$, respectively). The numbers of activated eosinophils in the nasal tissue increased significantly during the pollen season in both the zafirlukast and the placebo groups, but not in the BDP group. These results obtained with a limited number of patients do not support any clinical efficacy of regular treatment with an oral antileukotriene in seasonal allergic rhinitis but rather favor the use of a nasal glucocorticoid.

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Summary of Clinical Trials with Zafirlukast

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Zafirlukast is an orally active and selective cysteinyl leukotriene (cysLT) receptor antagonist. In humans, zafirlukast antagonized the effects of exogenously administered LTD_4 and cysLTs released endogenously in response to physical and chemical stimuli. Zafirlukast antagonized LTD_4-induced bronchoconstriction, with effects still evident 12 h after drug administration. In clinical models of asthma, zafirlukast inhibited bronchospasm after allergen or exercise challenge in patients with asthma. In multicenter trials in patients with chronic, stable asthma, zafirlukast reduced asthma symptoms, decreased as-needed agonist use, and improved pulmonary function without increasing the number of adverse events. Zafirlukast also exhibited evidence of an anti-inflammatory effect in the lung in preliminary studies involving segmental antigen challenge. The results from these clinical trials demonstrate that zafirlukast is effective and safe for the prophylactic treatment of asthma.

Drug Class:	Topical Immunomodulators (TIMS) a.k.a. Topical Calcineurin Inhibitors	
Drugs Reviewed:	**Pimecrolimus (Elidel®)**	**Tacrolimus (Protopic®)**

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently 2 topical immunomodulators available in the United States as indicated above
- There is currently 1 FDA approved indications for both of the topical immunomodulators. (see *Indications Table* that follows)
- Both of the immunomodulators are FDA approved for treatment of atopic dermatitis.
- Elidel® is currently available only as a cream; Protopic® is currently available only as an ointment.
- Pimecrolimus is available in the U.S. as an oral formulation, Prograf®, which is indicated for prophylactic therapy in liver or kidney transplants."
- Contraindications, warnings, adverse drug events, and drug interactions are similar for both topical immunomodulators and are considered class effects. Refer to *Class Effects* table for more details.

Summary of Indications [1,2,3]

Indication	Pimecrolimus	Tacrolimus
Atopic dermatitis	✓	✓
Allergic contact dermatitis	C	C
Irritant contact dermatitis	C	C

✓ = FDA approved indication C = Not FDA approved; however, studies indicate possible effectiveness

Place in Therapy [1-5]

- Both products are indicated for short-term and intermittent long-term treatment of atopic dermatitis only. Long term or continuous use is not approved.
- Both products received an indication for second line therapy.
- Elidel® is indicated for non-immunocompromised patients. Protopic® does not contain language in its indication about immunocompromised patients.
- Elidel® is indicated for mild-to-moderate atopic dermatitis. Protopic® is indicated for moderate-to-severe atopic dermatitis.
- Elidel® and Protopic® 0.03% are indicated in patients 2 years old and older. Protopic® 0.1% is indicated in adults only
- Neither product is recommended for use in infected dermatitis. Infections should be cleared before using either product.
- Neither product should be used concomitantly with therapies utilizing UV exposure. Patients should be advised to minimize or avoid natural or artificial sunlight exposure.
- Skin atrophy, a local adverse event, long associated with topical corticosteroids, was not seen in any of the clinical trials with pimecrolimus or tacrolimus. In contrast to topical corticosteroids, tacrolimus and pimecrolimus have been shown to be also safe for application to particularly sensitive areas such as the face and neck. Lack of skin atrophy is a major advantage over topical steroid formulations, particularly regarding use in children.
- A topical immunomodulator may be considered over topical steroids in infants and children; these patients are at risk of systemic complications from potent topical steroid formulation (e.g., adrenal suppression, intracranial hypertension, growth retardation). The overall efficacy/toxicity profile of topical pimecrolimus appears similar to that of topical tacrolimus in atopic dermatitis patients.[9]

Department of Veterans Affairs Formulary[6]

Neither topical immunomodulator is covered by the VA.

Summary of Pipeline Agents Expected to Offer Related Treatment Options[7]

Tacrolimus – topical cream formulation in Phase III trials (as of 2004)

Targretin (LGD-1069) - Bexarotene retinoid subtype receptor selective agonist – Topical gel formulation under development by Ligand Pharmaceuticals for treatment of moderate-to-severe atopic hand dermatitis (eczema). Phase I/II complete; Phase II/III registration trials planned for 2004 (as of 3/2004).

Class Effects:	Topical Immunomodulators (TIMS)
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology [1,2,4]	Though chemically dissimilar, the two agents have similar mechanisms of action. The exact mechanism of action in atopic dermatitis is not known. The actions below have been observed but the clinical significance of these observations in atopic dermatitis is not known. Both agents bind to the intracellular protein macrophilin-12 (FKBP-12), resulting in an inhibition of the phosphatase activity of calcineurin. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Both inhibit the release of inflammatory cytokines and mediators from skin mast cells.
Pediatric Labeling [1,2]	▪ Protopic®- 0.03% ointment for children aged 2 to 15 years (0.1% indicated for adults only) ▪ Elidel® - 2 years of age and older
Contraindications [1,2]	▪ Hypersensitivity to the agent or any component of the preparation ▪ Netherton's Syndrome – potential for increased systemic absorption ▪ Application to active cutaneous infections
Major AEs / Warnings [1,2,4,5]	▪ The most common adverse reactions are localized reactions (such as skin burning, stinging, soreness). These symptoms are generally mild to moderate in severity and typically resolve as the lesions of atopic dermatitis heal. ▪ While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with a topical immunomodulator may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits should be evaluated. ▪ Lymphadenopathy – In clinical studies lymphadenopathy has been reported for both agents. The cases were usually related to infections and noted to resolve upon appropriate antibiotic therapy. In the absence of a clear etiology or in the presence of acute infectious mononucleosis, consider discontinuation of the TIM. Monitor patients who develop lymphadenopathy to ensure that the lymphadenopathy resolves. ▪ Skin papillomas - consider discontinuing therapy if papillomas worsen or are not responding to conventional therapy ▪ Minimize/avoid exposure to natural or artificial sunlight ▪ The safety of Protopic® has not been established in patients with generalized erythroderma. ▪ Immunocompromised patients - Elidel® is indicated for non-immunocompromised patients. Protopic® does not contain language in its indication about immunocompromised patients.

Class Effects:	Topical Immunomodulators (TIMS)
Drug Interactions[1,2,4,5]	Formal topical drug interaction studies with PROTOPIC Ointment have not been conducted. Based on its minimal extent of absorption, interactions of PROTOPIC Ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.
Pregnancy[1,2]	Pregnancy Category C

Drug Class:	Topical Immunomodulators (TIMS)	
Characteristic	Pimecrolimus	Tacrolimus
	Elidel®	Protopic®
Date of FDA Approval[8]	December 13, 2001	December 8, 2000
Generic available?	No	No
Manufacturer (if single source)	Novartis	Fujisawa
Dosage forms / route of admin	Topical, Cream: 1%	Topical, Ointment: 0.03% and 0.1%
Dosing frequency	BID	BID
General dosing guidelines[1,2]	Apply a thin layer of Elidel cream to the affected skin twice daily. Elidel may be used on all skin surfaces, including the head, neck, and intertriginous areas. Elidel should be used twice daily for as long as signs and symptoms persist. Treatment should be discontinued if resolution of disease occurs. Elidel Cream should not be used with occlusive dressings.	**ADULT** Apply a thin layer of Protopic ointment 0.03% **or** 0.1% to the affected skin areas twice daily. **PEDIATRIC** Apply a thin layer of Protopic ointment 0.03% to the affected skin areas twice daily. Treatment should be continued for one week after clearing of signs and symptoms. Protopic ointment 0.03% and 0.1% should not be used with occlusive dressings.
FDA Labeled Indications[1,2]	The short-term and intermittent long-term therapy in the treatment of **mild to moderate** atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.	Both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated for short-term and intermittent long-term therapy in the treatment of patients with **moderate to severe** atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

Drug Class:	Topical Immunomodulators (TIMS)	
Characteristic	Pimecrolimus	Tacrolimus
	Elidel®	Protopic®
Other Studied Uses[3]	Allergic contact dermatitis Irritant contact dermatitis Psoriasis – occlusive dressings were used	Allergic contact dermatitis Irritant contact dermatitis Pruritis – uremic Psoriasis – occlusive dressings were used Rosacea
Pharmacokinetic Issues [1-3]	In adult patients being treated for atopic dermatitis [13%- 62% Body Surface Area (BSA) involvement] for periods up to a year, blood concentrations of pimecrolimus are routinely either at or below the limit of quantification of the assay (< 0.5 ng/mL). In those subjects with detectable blood levels they are routinely < 2 ng/mL and show no sign of drug accumulation with time. In general, the blood concentrations measured in adult atopic dermatitis patients were comparable to those seen in the pediatric population.	In clinical studies, peak tacrolimus blood concentrations have ranged from undetectable to 20 ng/mL after single or multiple doses of 0.1% Protopic ointment, with most patients having peak blood concentrations less than 5 ng/mL. The results from a pharmacokinetic study of 0.1% Protopic ointment in 20 pediatric (ages 6-13 years), show peak tacrolimus blood concentrations below 1.6 ng/mL in all patients. There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. In adults with an average of 53% BSA treated, exposure (i.e., AUC) of tacrolimus from Protopic is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood level at which systemic effects can be observed is not known.
Hepatic/Renal Impairment [1-3]	The effects of hepatic insufficiency or renal insufficiency on the pharmacokinetics of topically administered pimecrolimus have not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.	Low systemic exposure when administered topically. No specific recommendations for the need to alter dosage given by the manufacturer.

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Abstracts

Eur J Dermatol. 2003 Sep-Oct;13(5):455-61.

Non-steroidal topical immunomodulators provide skin-selective, self-limiting treatment in atopic dermatitis.

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Topical corticosteroids are the mainstay of treatment for atopic dermatitis; however, their clinical utility is limited by potential side effects. Recently, the steroid-free topical immunomodulators tacrolimus ointment and pimecrolimus cream have become available. These agents provide effective treatment without causing skin atrophy or other steroidal side effects, and their physiochemical properties, such as relatively large molecular size and high lipophilicity, limit diffusion through skin and into the bloodstream, providing skin-selective treatment. Clinical trials with more than 1,700 paediatric and adult patients have demonstrated that treatment with either agent is associated with minimal systemic absorption of tacrolimus or pimecrolimus. Additionally, studies have shown that percutaneous absorption of tacrolimus decreases as treatment continues and clinical improvement occurs. This self-limiting facet of the treatment, together with the skin-selectivity of topical immunomodulators, is reflected in the good safety and tolerability profiles of these agents, which promise to significantly improve the long-term management of atopic dermatitis.

Br J Dermatol. 2003. 148 (Suppl.63): 6-7. **(excerpted)**

International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies

Ellis C, Luger T, et al.

Pre-clinical and clinical findings

When discussing safety of the new topical calcineurin inhibitors, two aspects have to be considered:

- potential systemic exposure due to percutaneous absorption;
- and local adverse events.

Percutaneous absorption of tacrolimus in healthy volunteers has been shown to be generally low. Although in patients with atopic dermatitis, tacrolimus blood levels have been shown to be dose-dependent, broadly related to the severity of the disease and degree of lichenification the majority had low tacrolimus blood levels and these have shown to decrease over time.

Systemic blood levels of pimecrolimus have been shown to be consistently low and independent of duration of therapy (3 weeks to 1 year) and age of patients. There were no significant increases in systemic blood levels with increasing extent of body surface involvement (up to 92% TBSA). As with tacrolimus, no long-term accumulation has been reported with pimecrolimus. In the clinical trials both pimecrolimus and tacrolimus have shown no significant systemic toxicity.

Skin atrophy, a local adverse event, long associated with topical corticosteroids, was not seen in any of the clinical trials with pimecrolimus or tacrolimus. In contrast to topical corticosteroids, tacrolimus and pimecrolimus have been shown to be also safe for application to particularly sensitive areas such as the face and neck.

The most common important local-site reaction with topical tacrolimus and pimecrolimus is local discomfort associated with the application of the drug. In the tacrolimus clinical trials (with 0·03% ointment) up to 36% of paediatric patients and up to 47% of adult patients - exposed to the study medication experienced a local burning sensation at time of application. Pimecrolimus cream 1% demonstrated a comparable level of application-site burning to conventional treatment with only 7·4% vs. 7·4%, respectively, reporting burning sensation in the long-term paediatric studies.[61] Also, in adult patients 10·4% of the pimecrolimus group experienced application-site burning compared to 3·1% in the conventional treatment group. Application site burning is, however, transient and of short duration.

Given the mechanism of action, the possibility of local immunosuppression with topical tacrolimus and pimecrolimus is a potential concern. However, the risk of local bacterial infections is less in patients treated with topical calcineurin inhibitors than in patients on topical corticosteroids. It is important to note that corticosteroids act on a broad spectrum of immune competent cells, including Langerhans' cells that have a key function in the local immunosurveillance. In clinical studies with pimecrolimus secondary skin infections occurred at similar rates as those patients treated with placebo. With both compounds there is a decreased rate of skin infection over increasing length of use.

With tacrolimus ointment in a 52-week photocarcinogenicity study, the median time to onset of skin tumour formation was decreased in hairless mice as compared to vehicle-treated animals, following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment. The risk of photocarcinogenicity is still undetermined in humans. In a similar study with pimecrolimus, there was a decrease in median time to onset, with vehicle cream alone, but this was unchanged with the addition of pimecrolimus. It is nevertheless prudent for patients to minimize natural or artificial sunlight exposure whilst using the topical treatments.

In summary, the new topical calcineurin inhibitors seem to be extremely safe without many of the side-effects associated with conventional treatment for atopic dermatitis.

Dermatology. 2004;208(4):365-72.

Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis.

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BACKGROUND: Pimecrolimus cream 1% is a non-steroid, selective inflammatory cytokine inhibitor indicated for atopic dermatitis (AD). OBJECTIVE: To compare the safety and efficacy of pimecrolimus cream 1%-based treatment versus conventional therapy in adults with moderate AD. METHODS: Patients were randomized to receive pimecrolimus cream 1% (n = 62) or vehicle (n = 68) at the first signs/symptoms of AD, for 24 weeks as required. A moderately potent topical corticosteroid (prednicarbate 0.25% cream) was allowed in both groups to treat flares. RESULTS: Corticosteroids were required on fewer days in the pimecrolimus group, compared with the vehicle group (9.7 vs. 37.8%, $p < 0.001$). Furthermore, 59.7% of pimecrolimus-treated patients experienced no flares during the study period, compared with 22.1% of vehicle-treated patients ($p < 0.001$). Pimecrolimus cream 1% was well tolerated throughout the study. CONCLUSION: For adults with moderate AD, pimecrolimus cream 1% is well tolerated, reduces the incidence of flares, reduces/eliminates corticosteroid use, improves long-term disease control and enhances the patients' quality of life.

J Dermatolog Treat. 2003;14(Suppl 1):5-16.

Atopic dermatitis management with tacrolimus ointment (Protopic).

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Tacrolimus ointment is the first of a new class of non-steroidal topical immunomodulators indicated for the treatment of atopic dermatitis. Topical tacrolimus has been subject to an extensive clinical development program involving more than 16,000 patients. A clinical trial program, including vehicle-controlled studies, short- and long-term comparative studies and long-term safety studies, has investigated tacrolimus 0.1% and 0.03% ointment for the treatment of atopic dermatitis in adults and children aged 24 months and older. Tacrolimus monotherapy is rapidly effective, resulting in clinical improvements within three days of starting therapy, and produces a progressive increase in efficacy that is sustained during long-term treatment. Tacrolimus treats the signs and symptoms of atopic dermatitis, reduces the incidence of flares, and offers the potential for long-term disease control. No major safety concerns have been reported to date. Tacrolimus ointment is generally well tolerated, the primary adverse events being mild to moderate and transient application-site reactions: skin burning, pruritus and erythema. Tacrolimus ointment is a significant advance in dermatology and provides physicians with an alternative to conventional topical corticosteroid therapy.

Ann Allergy Asthma Immunol. 2003 Dec;91(6):563-6.

Topical pimecrolimus in the treatment of human allergic contact dermatitis.

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BACKGROUND: Contact dermatitis is a common clinical problem, with prevalent sensitizers being cosmetics, metals, medicines, and plants. Plants of the Toxicodendron species cause allergic contact dermatitis (ACD) in 50% to 70% of the population. Pimecrolimus is an ascomycin macrolactam developed for the treatment of inflammatory skin diseases and approved by the US Food and Drug Administration for atopic dermatitis. There are studies supporting the effectiveness of macrolactams when administered before antigen challenge, but there are no studies describing the effectiveness of these drugs in the treatment of established human ACD. OBJECTIVE: To investigate the effect of topical pimecrolimus in the treatment of Toxicodendron-induced ACD once rash is evident. METHODS: Poison ivy tincture was applied to the bilateral anterior forearms of 12 subjects with Finn Chambers (Allerderm Diagnostic Products, Petaluma, CA). After dermatitis was evident, volunteers treated each arm twice daily with either 1% topical pimecrolimus cream or placebo in a blinded fashion. Outcomes measured were a dermatitis grading score and time to rash and itch resolution. RESULTS: The median +/- SEM time for rash resolution was 16.55 +/- 1.59 days in the treatment group and 16.27 +/- 1.82 days in the placebo group (P = 0.601). The median time for itch resolution was 4.73 +/- 1.56 days in the treatment group and 4.91 +/- 1.59 days in the placebo group (P = 0.167). The average dermatitis score was 2.26 +/- 0.17 in the treatment group and 2.32 +/- 0.15 in the placebo group (P = 0.62). CONCLUSIONS: The application of topical pimecrolimus is ineffective in the treatment of ongoing Toxicodendron-induced ACD.

Br J Dermatol. 1998 Dec;139(6):992-6

The novel ascomycin derivative SDZ ASM 981* is effective for psoriasis when used topically under occlusion.

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Topical SDZ ASM 981 has been found to be highly effective in preclinical models of T-cell-mediated skin disease. T cell activation is crucial in the pathogenesis of psoriasis. It has been hypothesized that SDZ ASM 981 may prove to be an effective treatment for chronic plaque psoriasis. Therefore, the study objective was to determine the efficacy, tolerability and safety of the new topical macrolactam, SDZ ASM 981, for chronic plaque psoriasis. Ten patients with chronic plaque-type psoriasis were treated with SDZ ASM 981 (0.3% and 1.0%), the corresponding ointment base (placebo) and open-labelled clobetasol-17-propionate ointment (0.05%) in a randomized, double-blind, within-subject comparison for 2 weeks using the microplaque assay. Evaluation was performed by daily determination of clinical scores for erythema and induration. The results of the study showed that, after 2 weeks of treatment, total scores described by 92% for clobetasol, by 82% for 1 SDZ ASM 981, by 63% for 0.3% SDZ ASM 981 and by 18% for the ointment base (placebo). No adverse drug effects were seen in any patient throughout the study. We conclude from our results that the new macrolactam SDZ ASM 981 (1%) is similar to clobetasol-17-propionate (0.05%) in plaque-type psoriasis when applied topically under occlusion for 2 weeks using the microplaque assay.

*** SDZ ASM 981 = Pimecrolimus**

Drug Class:	Onychomycosis Oral Antifungals		
Drugs Reviewed:	terbinafine (Lamisil®)	itraconazole (Sporanox®)	griseofulvin (Gris-Peg®, Grifulvin®, Fulvicin®)

Class Summary: Indications, Class Effects, and Uniqueness [2,5-8]

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently three oral antifungals used for the treatment of onychomycosis available in the United States as indicated above.
- All of the antifungal agents are FDA approved for the treatment of onychomycosis.
- Short-term oral itraconazole and oral terbinafine therapy were found to be similar in efficacy and adverse effects in a randomized, double-blind comparative study for the treatment of toenail onychomycosis. There were less treatment-related serious adverse events in the itraconazole patients and more terbinafine-treated patients discontinued therapy permanently due to adverse events[5]. However, other studies have shown terbinafine to have better efficacy in treating toenail onychomycosis.
- In another trial (LION study) with long-term outcomes assessment, superior efficacy was observed with terbinafine. Both treatment groups had high relapse rates of 21% and 48% (terbinafine and itraconazole, respectively).
- In treatment of onychomycosis, the duration of treatment is less for terbinafine than griseofulvin. In a clinical comparison, terbinafine had better efficacy and a lower incidence of adverse effects when compared to griseofulvin.
- Contraindications, warnings, and adverse drug events and are somewhat similar for all of the oral antifungal agents and are considered class effects for itraconazole and terbinafine. Both drugs have drug interactions, although different ones. Refer to *individual monographs* for more details.

Summary of Indications [6-8]

terbinafine (Lamisil®)	itraconazole (Sporanox®)	Griseofulvin (Gris-Peg®, Grifulvin®, Fulvicin®)
▪ Treatment of onychomycosis of the toenail or fingernail caused by dermatophytes.	In non-immunocompromised: patients: ▪ Onychomycosis of the fingernail or toenail due to dermatophytes (tinea unguium) In immunocompromised and non-immunocompromised patients: ▪ Blastomycosis (pulmonary and extra-pulmonary) ▪ Histoplasmosis ▪ Aspergillosis (pulmonary and extra-pulmonary) in patients who are intolerant of or who are refractory to amphotericin B therapy	▪ Tinea capitis ▪ Tinea corporis ▪ Tinea pedis ▪ Tinea unguium (onychomycosis) ▪ Tinea cruris ▪ Tinea barbae
Prior to initiating treatment, obtain appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) to confirm the diagnosis of onychomycosis.		

Department of Veterans Affairs Formulary [3]

Itraconazole Oral
Terbinafine HCl Oral

Summary of Pipeline Agents Expected to Offer Related Treatment Options

Penecure – FDA has approved an IND application from Dimethaid Research Inc. for the company's topical antifungal treatment Penecure. Penecure uses Dimethaid's proprietary transcellular technology designed to minimize exposure to active drug and significantly lower the risk of side effects. The new product has already passed a proof-of-concept study at the University of California, as well as laboratory dose-ranging and accelerated stability studies. Unlike current antifungal lacquers, Penecure has demonstrated an ability to deliver clinically therapeutic levels of active drug through nails, directly targeting the disease site. (Excerpted from http://www.dimethaid.com/media/pdf/FDAPenecureNRFinaltemp.pdf, accessed 9/23/2004).

Drug Class:	Onychomycosis Oral Antifungals		
Characteristic	**terbinafine**	**itraconazole**	**griseofulvin**
	Lamisil®	Sporanox®	Gris-Peg®, Grifulvin®, Fulvicin®
Pharmacology [6-8]	Inhibits squalene oxidase which blocks the biosynthesis of ergosterol. Ergosterol is an essential component of fungal cell membranes.	Inhibits the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is an essential component of fungal cell membranes.	An antibiotic derived from a species of *Penicillium*, griseofulvin is fungistatic. It is deposited in keratin precursor cells and has a greater affinity for diseased tissue. Griseofulvin binds to the new keratin, making it resistant to fungal invasion.
Date of FDA Approval [1]	May 1996	September 1992	-----
Generic available?[1]	No	No	Previously there have been generics available. Currently there are availability issues with the generics.
Manufacturer (if single source)	Novartis	Janssen	Multiple
Dosage forms / route of administration [6-8]	**Tablet:** 250 mg (also available as a 1% topical solution, cream and gel but not indicated for the treatment of onychomycosis)	**Capsule:** 100 mg **Oral Solution:** 100 mg/10ml **IV:** 10 mg/ml	**Microsize tablets:** Fulvicin® U/F: 250, 500 mg; Grifluvin® V: 125, 250, 500 mg **Oral suspension:** Grifluvin® V: 125 mg/5 ml **Ultramicrosize tablets:** Gris-Peg® 125, 250 mg (Fulvicin® P/G – discontinued)
General dosing guidelines [6-8]	▪ Onychomycosis of fingernails: 250 mg daily x 6 weeks ▪ Onychomycosis of toenails: 250 mg daily x 12 weeks	▪ Onychomycosis of fingernails: 2 pulses of 250 mg BID for 1 week, with 3 weeks between pulses ▪ Onychomycosis of toenails ± fingernails: 250 mg daily x 12 weeks	Onychomycosis of fingernails ▪ Microsize – 1 gm daily x 4 months ▪ Ultramicrosize – 660 mg or 750 mg daily x 4 months Onychomycosis of toenails ▪ Microsize – 1 gm daily x 6 months ▪ Ultramicrosize – 660 mg or 750 mg daily x 6

Drug Class:	Onychomycosis Oral Antifungals		
Characteristic	**terbinafine**	**itraconazole**	**griseofulvin**
	Lamisil®	Sporanox®	Gris-Peg®, Grifulvin®, Fulvicin®
			months
Pediatric Labeling 6-8	Safety and efficacy have not been established in pediatric patients.	Safety and efficacy in children have not been established. Limited information available for use with: Solution in children 6 months and up and Capsules in children 3 years and up	Age 2 and older for other indications
Contraindications 4,6-8	▪ Hypersensitivity to terbinafine or any of its components.	▪ Itraconazole should not be used to treat onychomycosis in patients with CHF or a history of CHF. ▪ Coadministration with quinidine, triazolam, midazolam, pimozide, dofetilide, cisapride, or levacetylmethadol (levomethadyl). ▪ Coadministration with ergot alkaloids metabolized by CYP3A4 such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) ▪ Hypersensitivity to itraconazole or any of its components. ▪ HMG-CoA reductase inhibitors metabolized by the cytochrome P-3A4	▪ Hypersensitivity to griseofulvin ▪ Porphyria ▪ Hepatocellular failure ▪ Pregnancy or intent to become pregnant within one month from stopping therapy

Drug Class:	Onychomycosis Oral Antifungals		
Characteristic	**terbinafine**	**itraconazole**	**griseofulvin**
	Lamisil®	Sporanox®	Gris-Peg®, Grifulvin®, Fulvicin®
		system (e.g. Lovastatin, simvastatin). ▪ Treatment of onychomycosis in pregnancy or in women contemplating pregnancy.	
Drug interactions [4,6-8]	Terbinafine inhibits CYP2D6-mediated metabolism: cimetidine, rifampin, caffeine, cyclosporine, dextromethorphan.	Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of the cytochrome CYP3A4 enzyme system. cyclosporine, digoxin, oral hypoglycemics, protease inhibitors, warfarin, tacrolimus, zolpidem, calcium channel blockers (also some reports of increased edema), buspirone, carbamazepine, phenytoin, and vinca alkaloids.	Oral contraceptives, warfarin, phenobarbital, cyclosporine, salicylates
Major AEs/ Warnings [4, 6-8]	▪ Rare cases of liver failure – use in patients with chronic or active liver disease is not recommended ▪ Isolated reports of serious skin reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis). ▪ Changes to the ocular lens and retina – clinical significance not known ▪ Precipitation/exacerbation of cutaneous or systemic lupus erythematosus (infrequent) ▪ Transient decreases in absolute lymphocyte counts – clinical	▪ Rare cases of liver failure ▪ Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with itraconazole ▪ In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. ▪ If neuropathy occurs that may be attributable to itraconazole, the treatment	▪ Photosensitivity – avoid exposure to intense natural or artificial sunlight ▪ Lupus erythematosus or lupus like syndromes have been reported ▪ Hypersensitivity-type reactions, including rash, urticaria, angioneurotic edema (rare) ▪ Paresthesias of the hands and feet – rare after extended therapy ▪ Occasionally – N/V/D, oral thrush, HA, fatigue, dizziness, insomnia, mental confusion ▪ Proteinuria, leucopenia - rarely

Drug Class:	Onychomycosis Oral Antifungals		
Characteristic	**terbinafine**	**itraconazole**	**griseofulvin**
	Lamisil®	Sporanox®	Gris-Peg®, Grifulvin®, Fulvicin®
	significance unknown ▪ Neutropenia – severe and isolated, reversible upon discontinuation of terbinafine	should be discontinued. ▪ Concomitant administration of itraconazole and nevirapine is not recommended	
Pharmacokinetic issues [6-8]	▪ Well absorbed with the first pass metabolism significantly decreases bioavailability (to roughly 40%). ▪ Administration with food slightly increases bioavailability (area under the curve increased by < 20%).	▪ Cannot use the solution and the capsules interchangeably (increased bioavailability with the solution). ▪ The capsules should be taken after a full meal. The solution should be taken on an empty stomach. ▪ Grapefruit juice may reduce bioavailability of itraconazole. Decreased absorption with decreased gastric acidity (PPIs, H2 antagonists and antacids).	▪ Absorption can vary from person to person. A high fat meal increases the rate, but not the extent of absorption. ▪ The absorption of the ultramicrosize is 1.5 times more efficient than the microsize (only 2/3 of the dose of the ultramicrosize is needed). There is no evidence this causes any significant clinical differences in safety or efficacy.
Dosage adjustment in key populations [4, 6-8]	Patients with cirrhosis or renal impairment (ClCr = 50 ml/min) have shown a 50% decrease in terbinafine clearance. Use in these patients is not recommended.	Elderly – use is recommended in the elderly only if the potential benefits outweigh the potential risks. Pediatric use – limited information with pediatric use – safety and efficacy have not been established. Dosage adjustments of itraconazole are not required in patients with renal impairment.	Pediatrics – ultramicronized dose – 7.3 mg/kg/day (3.3 mg/lb per day)

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7. Product Information: Lamisil(R), terbinafine (tablets). Novartis Pharmaceuticals, East Hanover, NJ, (revised 1/2004) reviewed 9/2004.
8. Product Information: Sporonox(R), itraconazole capsules. Janssen Pharmaceutica, Titusville, NJ (PI revised 1/2004) reviewed 9/2004.

Abstracts

Am J Clin Dermatol. 2003;4(1):39-65.

Terbinafine: a review of its use in onychomycosis in adults.

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Terbinafine, an orally and topically active antimycotic agent, inhibits the biosynthesis of the principal sterol in fungi, ergosterol, at the level of squalene epoxidase. Squalene epoxidase inhibition results in ergosterol-depleted fungal cell membranes (fungistatic effect) and the toxic accumulation of intracellular squalene (fungicidal effect). Terbinafine has demonstrated excellent fungicidal activity against the dermatophytes and variable activity against yeasts and non-dermatophyte molds in vitro. Following oral administration, terbinafine is rapidly absorbed and widely distributed to body tissues including the poorly perfused nail matrix. Nail terbinafine concentrations are detected within 1 week after starting therapy and persist for at least 30 weeks after the completion of treatment. Randomized, double-blind trials showed oral terbinafine 250 mg/day for 12 or 16 weeks was more efficacious than itraconazole, fluconazole and griseofulvin in dermatophyte onychomycosis of the toenails. In particular, at 72 weeks' follow-up, the multicenter, multinational, L.I.ON. (Lamisil vs Itraconazole in ONychomycosis) study found that mycologic cure rates (76 vs 38% of patients after 12 weeks' treatment; 81 vs 49% of recipients after 16 weeks' therapy) and complete cure rates were approximately twice as high after terbinafine treatment than after itraconazole (3 or 4 cycles of 400 mg/day for 1 week repeated every 4 weeks) in patients with toenail mycosis. Furthermore, the L.I.ON. Icelandic Extension study demonstrated that terbinafine was more clinically effective than intermittent itraconazole to a statistically significant extent at 5-year follow-up. Terbinafine produced a superior complete cure rate (35 vs 14%), mycologic cure rate (46 vs 13%) and clinical cure rate (42 vs 18%) to that of itraconazole. The mycologic and clinical relapse rates were 23% and 21% in the terbinafine group, respectively, compared with 53% and 48% in the itraconazole group. In comparative clinical trials, oral terbinafine had a better tolerability profile than griseofulvin and a comparable profile to that of itraconazole or fluconazole. Post marketing surveillance confirmed terbinafine's good tolerability profile. Adverse events were experienced by 10.5% of terbinafine recipients, with gastrointestinal complaints being the most common. Unlike the azoles, terbinafine has a low potential for drug-drug interactions. Most pharmacoeconomic evaluations have shown that the greater clinical effectiveness of oral terbinafine in dermatophyte onychomycosis translates into a cost-effectiveness ratio superior to that of itraconazole, fluconazole and griseofulvin. CONCLUSION: Oral terbinafine has demonstrated greater effectiveness than itraconazole, fluconazole and griseofulvin in randomized trials involving patients with onychomycosis caused by dermatophytes. The drug is generally well tolerated and has a low potential for drug interactions. Therefore, terbinafine is the treatment of choice for dermatophyte onychomycosis.

Arch Dermatol. 2002 Jun;138(6):811-6.

Oral treatments for toenail onychomycosis: a systematic review.

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OBJECTIVE: To identify and synthesize the evidence for the efficacy of oral treatments for fungal infections of the toenails. DESIGN: Systematic review of randomized controlled trials. INTERVENTIONS: Oral treatments for dermatophyte infections of the toenails. MAIN OUTCOME MEASURES: Cure confirmed by microscopy and culture results in patients with clinically diagnosed fungal infections. Data relating to the clinical cure rates were also extracted from the trials. RESULTS: A pooled analysis of 2 trials comparing mycological cure rates from continuous treatment with terbinafine (250 mg/d for 12 weeks) and continuous treatment with itraconazole (200 mg/d for 12 weeks) found a statistically significant difference in 11- and 12-month outcomes in favor of terbinafine (risk difference, -0.23 [95% confidence interval, -0.32 to -0.15]; number needed to treat, 5 [95% confidence interval, 4 to 8]). An analysis of clinical cure rates was not possible because of the diversity of definitions used in researching the effectiveness of oral antifungal drugs for onychomycosis. Only 3 trials gave a clear definition of clinical cure and presented data for these outcomes. CONCLUSIONS: There is good evidence that a continuous regimen of terbinafine (250 mg/d) for 3 months is the most effective oral treatment for fungally infected toenails. Consensus among researchers evaluating oral antifungal drugs for onychomycosis is needed to establish meaningful definitions of clinical cure. Most trials were funded by the pharmaceutical industry; we found little independent research, and this may have introduced bias to the review.

Br J Dermatol. 2001 Sep;145(3):446-52.

Long-term efficacy of antifungals in toenail onychomycosis: a critical review.

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BACKGROUND: Modern antifungal drugs achieve high mycological and clinical cure rates in onychomycosis of the toes, but little is known about the long-term evolution of the treated patients. OBJECTIVES: The aim of this review was to analyse the therapeutic results recorded more than 1 year after initiation of therapy. METHODS: We used two endpoints for the analysis: EP1 (the number of patients with negative mycology after follow-up, divided by the number of patients included at day 0, including all patients lost to follow-up), and EP2 (the number of patients with negative mycology after follow-up divided by the number of patients with negative mycology at week 48). Clinical cure rate (EPclin) was the number of patients clinically cured or with minimal residual lesions divided by the number of patients included at day 0. RESULTS: From a Medline search we identified 17 studies providing results beyond 48 weeks. Ketoconazole 200 mg d(-1) up to 1 year resulted in EP1 of 11% at 18 months, and EP2 of 43%. Griseofulvin 1 g d(-1) for 1 year allowed an EP1 of 43% at 18 months, and EP2 of 71%. The mean EP1 after fluconazole once weekly up to 1 year was 49% at 18 months, and EP2 was 91%. With itraconazole 200 mg d(-1) or 400 mg d(-1) for 1 week each month for 3-4 months, EP1 was 37% at 18 months, and 53% at 2 years; EP2 was 76% at 4 years. Terbinafine 250 mg d(-1) for 12-16 weeks achieved an EP1 of 62% at 18 months, 72% at 2 years, and 60% at 4 years; EP2 was 80% at 18 months, 81% at 2 years, and 71% at 4 years. In the only study planned to compare the long-term efficacy of terbinafine and itraconazole, EP1 at 18 months was significantly higher with continuous terbinafine than with intermittent itraconazole (66% vs. 37%, $P < 0.001$). The clinical cure rates were 21% at 60 weeks and 37% at 72 weeks with fluconazole. EPclin was 27% at 18 months and 35% at 2 years with itraconazole. EPclin was 48% at 18 months, 69% at 2 years and 50% at 4 years with terbinafine. CONCLUSIONS: Considering the stringency of the criteria we used, this critical review suggests that the long-term efficacy achieved with terbinafine is superior to that obtained with griseofulvin, ketoconazole, fluconazole or itraconazole.

Dermatology. 2001;202(3):235-8.

Efficacy of itraconazole, terbinafine, fluconazole, griseofulvin and ketoconazole in the treatment of Scopulariopsis brevicaulis causing onychomycosis of the toes.

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BACKGROUND: Scopulariopsis brevicaulis is a common non-dermatophyte mould that can cause onychomycosis. OBJECTIVE: To evaluate the efficacy and safety of the oral antifungal agents griseofulvin, ketoconazole, itraconazole, fluconazole and terbinafine in the treatment of S. brevicaulis. PATIENTS AND METHODS: In a prospective, comparative, parallel-group, single-blinded, randomized, non-industry-sponsored study, patients with toe onychomycosis caused by S. brevicaulis sp. were randomized and treated with one of 5 oral antifungal agents, i.e. griseofulvin, ketoconazole, itraconazole (pulse), fluconazole or terbinafine. The treatment regimens were: griseofulvin 600 mg twice daily for 12 months, ketoconazole 200 mg daily for 4 months, itraconazole pulse therapy given for 3 pulses, with each pulse consisting of 200 mg twice daily for 1 week with 3 weeks off between successive pulses, terbinafine 250 mg daily for 12 weeks and fluconazole 150 mg daily for 12 weeks. RESULTS: There were 59 patients (48 males, 11 females, mean age 35.6 years, range 25-53 years). All patients had clinical evidence of distal and lateral onychomycosis, with moderate to severe disease of the target nail. Between the treatment groups there was no significant difference in the mean age of the patients or the mean area of involvement with onychomycosis at baseline. The efficacy parameters were clinical cure (CC) and mycological cure (MC). At month 12 after the start of treatment, the response was: griseofulvin, CC 3/11, MC 0/11, CC + MC 0/11; ketoconazole, CC 10/12, MC 8/12, CC + MC 8/12; itraconazole, CC 12/12, MC 12/12, CC + MC 12/12; terbinafine, CC 12/12, MC 11/12, CC + MC 11/12, and fluconazole, CC 8/12, MC 8/12, CC + MC 8/12. Adverse effects consisted of: griseofulvin, gastro-intestinal symptoms, allergic reaction, photodermatitis, hepatic and renal dysfunction in 11 patients with discontinuation of treatment in 3 patients; ketoconazole, hepatic dysfunction but no symptomatic changes in 2 patients; itraconazole, nausea and vomiting in 2 patients; terbinafine, taste disturbance in 2 patients, nausea in 3 patients, and fluconazole, severe gastro-intestinal events in 5 patients. None of the patients receiving ketoconazole, itraconazole, terbinafine or fluconazole discontinued treatment. CONCLUSIONS: Itraconazole and terbinafine demonstrate efficacy against some cases of S. brevicaulis toe onychomycosis. These agents also appear to be safe in the course of therapy for toe onychomycosis. Griseofulvin is ineffective against toe onychomycosis caused by S. brevicaulis. Ketoconazole is not recommended for toe onychomycosis given its potential for adverse effects, particularly with the availability of the newer antifungal agents.

Drug Saf. 2000 Jan;22(1):33-52.

A risk-benefit assessment of the newer oral antifungal agents used to treat onychomycosis.

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The newer antifungal agents itraconazole, terbinafine and fluconazole have become available to treat onychomycosis over the last 10 years. During this time period these agents have superseded griseofulvin as the agent of choice for onychomycosis. Unlike griseofulvin, the new agents have a broad spectrum of action that includes dermatophytes, Candida species and nondermatophyte moulds. Each of the 3 oral antifungal agents, terbinafine, itraconazole and fluconazole, is effective against dermatophytes with relatively fewer data being available for the treatment of Candida species and nondermatophyte moulds. Itraconazole is effective against Candida onychomycosis. Terbinafine may be more effective against C. parapsilosis compared with C. albicans; furthermore with Candida species a higher dose of terbinafine or a longer duration of therapy may be required compared with the regimen for dermatophytes. The least amount of experience in treating onychomycosis is with fluconazole. Griseofulvin is not effective against Candida species or the nondermatophyte moulds. The main use of griseo-fulvin currently is to treat tinea capitis. Ketoconazole may be used by some to treat tinea versicolor with the dosage regimens being short and requiring the use of only a few doses. The preferred regimens for the 3 oral antimycotic agents are as follows: itraconazole - pulse therapy with the drug being administered for 1 week with 3 weeks off treatment between successive pulses; terbinafine - continuous once daily therapy; and fluconazole - once weekly treatment. The regimen for the treatment of dermatophyte onychomycosis is: itraconazole - 200mg twice daily for I week per month x 3 pulses; terbinafine - 250 mg/day for 12 weeks; or, fluconazole - 150 mg/wk until the abnormal-appearing nail plate has grown out, typically over a period of 9 to 18 months. For the 3 oral antifungal agents the more common adverse reactions pertain to the following systems, gastrointestinal (for example, nausea, gastrointestinal distress, diarrhoea, abdominal pain), cutaneous eruption, and CNS (for example, headache and malaise). Each of the new antifungal agents is more cost-effective than griseofulvin for the treatment of onychomycosis and is associated with high compliance, in part because of the shorter duration of therapy. The newer antifungal agents are generally well tolerated with drug interactions that are usually predictable.

Drug Class:	Quinolones: Second-Generation			
Drugs Reviewed:	ciprofloxacin (Cipro®)	lomefloxacin (Maxaquin®)	norfloxacin (Noroxin®)	ofloxacin (Floxin®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

There are currently four second-generation quinolones available in the United States as indicated above.

- The fluoroquinolones are effective in treating both gram-positive and gram-negative infections. Currently, ciprofloxacin has the most FDA approved indications.
- All of the fluoroquinolones are effective in treating urinary tract infections caused by susceptible organisms.
- Ofloxacin, ciprofloxacin, and trimethoprim- sulfamethoxazole share similar overall gram-negative and gram-positive bacterial in vitro susceptibility (82%, 80%, 79%); however, significant differences do exist between different pathogens.

Ciprofloxacin: Only fluoroquinolone available as a suspension. Previously, ciprofloxacin was the most active fluoroquinolone against *P. aeruginosa*. Recent in vitro evidence suggests levofloxacin and gatifloxacin are as active against *P. aeruginosa* as ciprofloxacin. Ciprofloxacin remains effective in treating both urinary tract and systemic infections caused by *P. aeruginosa*, however the use of this agent continues to be limited by the increasing rates of resistance.

Norfloxacin is an effective treatment for uncomplicated and complicated urinary tract infections, but is not recommended as a first-line agent. Although norfloxacin achieves serum concentrations high enough for the treatment of many systemic infections following oral administration, newer quinolones have generally replaced it for the treatment of systemic infections. Other places in therapy where norfloxacin has been used include gastrointestinal infections, due to its pronounced activity against pathogens responsible for most diarrheal diseases (*Salmonella, Shigella, Campylobacter, Yersinia* and *E. coli*). In respiratory tract infections, norfloxacin has poor activity against *S. pneumoniae* and is not recommended as alternative to other agents with activity against pneumococci; rather, the drug should be indicated in selected cases secondary to gram-negative pathogens.

Ofloxacin: Ofloxacin has a broad spectrum of activity in vitro including *S. pneumoniae, H. influenzae, Branhamella (Moraxella) catarrhalis*, atypical pathogens such as *M. pneumoniae, L. pneumophila*, and enterobacteraceae. Due to the increasing development of resistance, ofloxacin should not be used as empiric therapy. Ofloxacin should be reserved for targeted indications where there is culture and sensitivity data guiding appropriate therapy.

Efficacy

Gram positive organisms: As a class, the third generation quinolones (Avelox®, Tequin® and Levaquin®) have superior activity against *S.pneumoniae* in comparison to Cipro®, Noroxin® , Floxin® and Maxaquin®. The second generation quinolones have activity against *S. aureus* (Methicillin sensitive), but the newer third generation and fourth generation agents appear to be more potent.

Gram Negative: Ciprofloxacin has been accepted as the most active against *Pseudomonas aeruginosa* and is capable of reaching concentrations high enough for use in systemic pseudomonal infections. Other second generation quinolones are not recommended for use in systemic pseudomonal infections, but may be used in the treatment of urinary tract infections of *Pseudomonas aeruginosa* where higher concentrations of the drug can be reached. Recent in vitro evidence suggests that the third generation fluoroquinolones, levofloxacin (Levaquin®) and gatifloxacin (Tequin®) are as active against *P. aeruginosa* as ciprofloxacin.

Atypical organisms: All quinolones (minus the first generation) have coverage against atypicals such as *Mycoplasma pneumoniae, Chlamydia* spp, and *Legionella* spp. For the treatment of atypical pneumonias, macrolides are likely to be equivalent to fluoroquinolones and are currently more cost-effective. Quinolones provide exceptional coverage against atypical pathogens when infection with these organisms is suspected in patients with community-acquired pneumonia.

However, ofloxacin has been associated with treatment failures, and ciprofloxacin has displayed reduced activity against Chlamydia species.

Adverse Events

Gastrointestinal adverse events (ranked from highest to lowest): Moxifloxacin (Avelox®) > Gatifloxacin (Tequin®) > Ciprofloxacin (Cipro®) > Norfloxacin (Noroxin®) > Ofloxacin (Floxin®) > Levofloxacin (Levaquin®)

CNS adverse events (ranked from highest to lowest): Norfloxacin (Noroxin®), Gatifloxacin (Tequin®) > Moxifloxacin (Avelox®) > Ciprofloxacin (Cipro®) > Ofloxacin (Floxin®) > Levofloxacin (Levaquin®)

Dermatologic/Phototoxicity: Lomefloxacin (Maxaquin®) appears to have the greatest potential for phototoxicity. Gatifloxacin (Tequin®), moxifloxacin (Avelox®) and levofloxacin (Levaquin®) appear to have the lowest potential for inducing phototoxicty.

Summary of Indications

ciprofloxacin	lomefloxacin	norfloxacin	ofloxacin
Cipro®	Maxaquin®	Noroxin®	Floxin®
▪ Susceptible infections due to *Enterococcus faecalis, S. saprophyticus, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa* ▪ Anthrax - Post exposure Prophylaxis ▪ Anthrax - Post exposure Management ▪ Bone And Joint Infections ▪ Bronchitis ▪ Conjunctivitis - Bacterial (topical) ▪ Corneal Ulcers (topical) ▪ Gonorrhea ▪ Infectious Diarrhea ▪ Intra-Abdominal Infections, complicated ▪ Lower Respiratory Tract Infections ▪ Otitis Externa (otic solution) ▪ Prostatitis, chronic bacterial ▪ Sinusitis ▪ Skin And Skin Structure Infections ▪ Typhoid Fever ▪ Urinary Tract Infections ▪ **Cipro XR** – Urinary tract infections and acute uncomplicated polynephritis	▪ Susceptible infections due to *H. influenzae, M. catarrhalis, E. coli, K. pneumoniae, P. mirabilis, S. saprophyticus, P. aeruginosa* ▪ Chronic bronchitis, acute bacterial exacerbation (not if *S. pneumoniae* is probable causative organism) ▪ Urinary tract infections, complicated and uncomplicated ▪ Urinary tract infection prophylaxis for transurethral surgery and transrectal prostate biopsy	▪ Uncomplicated urinary tract infections (including cystitis) due to *E. faecalis*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, S. *epidermidis*, *S.saprophyticus*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *P. vulgaris*, *S. aureus*, or *S. agalactiae*. ▪ Complicated urinary tract infections due to *E. faecalis*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, or *S. marcescens*. ▪ Prostatitis due to *E. coli*.	▪ Susceptible infections due to *S. pneumoniae, S. aureus, S. pyogenes, H. influenzae, P. mirabilis, N gonorrhoeae, C. trachomatis, E. coli, K. pneumoniae, P. aeruginosa* ▪ Chronic bronchitis, acute exacerbation ▪ Community-acquired pneumonia ▪ Conjunctivitis/corneal ulcers (ophthalmic solution) ▪ Cystitis, uncomplicated ▪ Gonorrhea, uncomplicated urethral and cervical ▪ Nongonococcal urethritis and cervicitis (*chlamydia*) ▪ Otitis media, acute with tympanostomy tubes (otic solution) ▪ Otitis media, chronic suppurative with perforated tympanic membranes (otic solution) ▪ Otitis externa (otic solution) ▪ Pelvic inflammatory disease ▪ Prostatitis ▪ Skin/skin structure infection, uncomplicated ▪ Urinary tract infections, complicated ▪ Mixed infections of urethra and cervix

Place in Therapy

Gonorrhea: Quinolone-resistant *N. gonorrhoeae* is a continuing problem. Quinolone antibiotics should not be used for infections acquired in Asia or the Pacific (including Hawaii), and use for infections acquired in California may be inadvisable; surveillance for antimicrobial resistance is important for guiding therapy recommendations in the treatment of *N. gonorrhoeae* (CDC, 2002).

Respiratory Tract Infections: Because of concerns regarding emerging resistance, fluoroquinolones with antipneumococcal activity should be reserved as second-line agents in the treatment of community-acquired pneumonia. According to a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (Heffelfinger et al, 2000), the use of fluoroquinolones in community-acquired pneumonia should be limited to adults under the following circumstances:

- Patients in which initial therapy with a suitable empirical antipneumococcal agent has failed.
- Patients who are allergic to suitable alternative agents.
- Patients who have a documented infection with a highly resistant pneumococci; penicillin MIC greater = to 4 µg/mL.

Ofloxacin has been effective in the treatment of respiratory tract infections. ACUTE BRONCHITIS is generally due to pneumococci and ofloxacin will not replace beta-lactam antibiotics as drug of first choice in these cases. However, ofloxacin and other quinolones may be useful in the treatment of bronchitis due to gram-negative organisms when beta-lactams or erythromycin have failed. Beta-lactams, macrolides, or cotrimoxazole (sulfamethoxazole and trimethoprim) will continue to be drugs of first choice for community-acquired pneumonia; however, ofloxacin and other quinolones may become initial therapy for hospital-acquired gram-positive pneumonia. Ofloxacin is similar in efficacy to amoxicillin for otorhinolaryngological infections; however the drug is unlikely to replace the beta-lactams in these infections (Anon, 1991).

Urinary Tract Infections: Cotrimoxazole is the recommended standard therapy for uncomplicated urinary tract infections in women. Trimethoprim and fluoroquinolones have similar efficacy. Fluoroquinolones are not recommended as initial empirical therapy due to issues of cost, as well as restricting use to prevent the development of resistance. Fluoroquinolones may be considered in communities with high rates (greater than 10% to 20%) of cotrimoxazole resistance.

Prostatitis: Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue. When taken for four to six weeks, norfloxacin, ciprofloxacin, levofloxacin, and ofloxacin have eradication rates of 67 to 91 percent. Ciprofloxacin should be reserved for use in patients with resistant gram-negative, pseudomonal prostatitis because of its superior activity against *P. aeruginosa*.

Acute sinusitis: The U.S. Food and Drug Administration (FDA) has labeled ciprofloxacin (Cipro®), gatifloxacin (Tequin®), moxifloxacin (Avelox®), and levofloxacin (Levaquin®) for use in the treatment of acute bacterial sinusitis. Clinical trials comparing fluoroquinolones with amoxicillin-clavulanate potassium (Augmentin®), cefuroxime axetil (Ceftin®), and clarithromycin (Biaxin®) have demonstrated the efficacy of the quinolone antibiotics. Generally quinolones are considered second line agents in the treatment of acute sinusitis.

Sexually Transmitted Diseases (Based on 2002 CDC guidelines): Ofloxacin 400 mg po single dose or levofloxacin 250 mg PO single dose are considered drugs of choice for uncomplicated gonococcal infections, while gatifloxacin 400 mg PO single dose or lomefloxacin 400 mg PO single dose are considered alternative therapy. In the treatment of chlamydial infections, ofloxacin 300 mg PO bid x 7 days or levofloxacin 500 mg PO qd x 7 days are considered alternative therapy. In the treatment of epididymitis, ofloxacin 300 mg PO bid or levofloxacin 500 mg PO qd are considered alternative therapy.

Department of Veterans Affairs Formulary

- Ciprofloxacin (2nd)
- Gatifloxacin (3rd)

Summary of Pipeline Agents Expected to Offer Related Treatment Options

Garenoxacin (Toyama Chemical/Schering-Plough) - des-fluoroquinolone antibiotic for treatment of respiratory infections, including chronic bronchitis, community-acquired pneumonia and acute maxillary sinusitis; once-daily oral and intravenous formulations. Phase III complete; NDA submission planned for late 2005 (as of 6/2004).

Levofloxacin oral solution formulation - NDA Submitted 12/2003 - Estimated User Fee Goal 10/2004

Prulifloxacin (Optimer Pharmaceuticals) - fluoroquinolone antibiotic with activity against gram-positive and gram-negative organisms for treatment of community-acquired respiratory tract infections and urinary tract infections. Phase III (as of 2004); NDA submission predicted for 4Q:05 (as of 2004).

Class Effects:	Quinolones: Second-Generation
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Quinolones affect bacterial cells by interfering with DNA and the enzyme DNA gyrase (topoisomerase IV). The formation of the quinolone-gyrase-DNA complex prevents the DNA polymerase from proceeding at the replication fork, thus stopping DNA synthesis.
Spectrum (innovator drug)	▪ Ciprofloxacin has a wide range of in vitro activity including both gram-positive and gram-negative organisms. In vitro activity has been demonstrated against *Escherichia coli, Klebsiella* spp, *Enterobacter* spp, *Citrobacter* spp, *Edwardsiella tarda*, *Salmonella* spp, *Shigella* spp, *Proteus mirabilis, Proteus vulgaris, Providentia stuartii, Providencia rettgeri, Morganella morganii, Serratia* spp, *Yersinia enterocolitica, Pseudomonas aeruginosa, Acinetobacter* spp, *Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus ducreyi, Neisseria gonorrhea, Neisseria meningitidis, Moraxella catarrhalis, Campylobacter* spp, *Aeromonas* spp, *Vibrio* spp, *Brucella melitensis, Pasturella multocida, Legionella* spp, *Staphylococcus aureus, Staphylococcus epidermidis, Streptococci pyogenes, Streptococci pneumoniae. Mycobacterium tuberculosis, Chlamydia trachomatis*, and most strains of streptococci are moderately susceptible to ciprofloxacin. Ciprofloxacin may have a role in therapy of atypical mycobacterial infections. ▪ Most anaerobic bacteria (including *Bacteroides fragilis and Clostridium difficile*), most strains of *Pseudomonas cepacia*, and some strains of *Pseudomonas maltophilia (Xanthomonas maltophilia)* are resistant to ciprofloxacin. ▪ Despite its excellent in vitro activity, several cases of resistance of *Pseudomonas, Enterobacteraceae*, staphylococci, and *Campylobacter* species to ciprofloxacin have been reported which may limit the drug's usefulness in further clinical trials. Combination of the drug with other agents to prevent the emergence of resistance needs to be evaluated. ▪ Ciprofloxacin and ofloxacin have been compared on numerous occasions on their antipseudomonal activity. Ciprofloxacin has lower *Pseudomonas aeruginosa* minimum inhibitory concentrations (MIC) in comparison to ofloxacin (0.25 mg/L versus 1 mg/L, respectively) therefore considered the more active than ofloxacin. However, ofloxacin has a more favorable pharmacokinetic profile (eg, longer half-life, greater area under the plasma concentration-time curve). In an in vitro comparison of ciprofloxacin and ofloxacin using pharmacokinetic and pharmacodynamic parameters (e.g., area under the inhibitory curve), ciprofloxacin was still favored over ofloxacin as an antipseudomonal agent. Despite these differences, single agent quinolone therapy is not recommended in the treatment of *Pseudomonas* infections with the exception of urinary tract infections. ▪ Ciprofloxacin has poor activity against vancomycin-susceptible and vancomycin-resistant enterococci. In one study, the minimum inhibitory concentration for 50% of the isolates tested was above the breakpoint for ciprofloxacin susceptibility. The emergence of enterococci resistance ciprofloxacin may be a function of its usage pattern against this organism. Quinolones, especially when used alone, are not recommended for enterococci infections. ▪ Bacterial susceptibility to the quinolones and resistance patterns are likely to change with clinical usage. In addition, pathogen susceptibility to ofloxacin is likely to change from institution to institution It is critical to confirm microbiologic diagnosis, carefully follow bacterial susceptibility data, and consider streamlining antibiotic therapy in patients treated with ofloxacin; otherwise, resistance to quinolone therapy is likely to follow.

Class Effects:	Quinolones: Second-Generation
Pediatric Labeling	Safety and efficacy has not been established in children under 18 years old for norfloxacin, lomefloxacin and ofloxacin and Cipro XR. Ciprofloxacin (regular release) is indicated for use in children (1 to 17 years of age) for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*. (Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.) Ciprofloxacin is indicated in pediatric patients to reduce the incidence or progression of disease following exposure to aerosolized anthrax (*Bacillus anthracis*). Clinical reviews and studies of children and infants have shown that intravenous or oral ciprofloxacin does not cause defects in linear growth, osteoarticular problems, or joint deformities.
Contraindications	▪ Hypersensitivity to any fluoroquinolones. ▪ Norfloxacin has an additional contraindication of history of tendonitis or tendon rupture on fluoroquinolone therapy. This a legacy of norfloxacin being the first second-generation quinolone approved. The severe fluoroquinolone-induced arthropathy observed in animals is not clearly documented to occur in adults and adolescents exposed to the drugs. All fluoroquinolones are associated with an increased (but low) risk of Achilles tendon rupture.
Major Adverse Effects / Warnings	GI and CNS are the most common adverse events; they are usually mild and may resolve with continued treatment. **Phototoxic reactions** (those that may develop within hours of drug administration) may occur in any patient who has received sufficient drug dosage and sufficient ultraviolet (UV) light. Photosensitivity reactions are immune mediated and require previous exposure to the offending agent and take usually 1-2 days to develop. Immune related reactions are rare with fluoroquinolones; phototoxic reactions are more common and appear to be a class effect that can develop when given in dosages that reach high enough tissue concentrations. Although the phototoxicity is a class reaction, the drugs differ significantly in the degree of phototoxicity potential. **Arthropathy**: The severe fluoroquinolone-induced arthropathy observed in animals is not clearly documented to occur in adults and adolescents exposed to the drugs. Although arthralgia with or without effusions was reported, it occurred at a relatively low rate (< 1.5%) and completely resolved after discontinuation of drug therapy, with no evidence of long-term or serious sequelae. Although only ciprofloxacin is FDA approved for children (for very limited indications), therapy with the drugs in this population appears to be justified on the basis of risk versus benefit considerations in compelling clinical circumstances (e.g., patients with cystic fibrosis with multidrug-resistant gram-negative infection). All fluoroquinolones are associated with an increased risk of Achilles tendon rupture, and that increase is true across the board for exposure to any fluoroquinolone. Risk factors include patients over 60 years of age, renal failure, dialysis, concomitant corticosteroid therapy, and dyslipidemia. **Cardiotoxicity – QT wave prolongation**: The FDA recommends in the package insert of all fluoroquinolones to have a warning statement suggesting that the risk of arrhythmias may be reduced by avoiding their use or administering them with caution in patients with known underlying cardiac conditions, those with known QTc interval prolongation or history of significant cardiac arrhythmias, those with uncorrected hypokalemia, and those receiving concomitant therapy with agents known to increase the QTc interval or to cause bradycardia (metoclopramide, cisapride, erythromycin, classes Ia and III antiarrhythmics, and tricyclic antidepressants). **Peripheral Neuropathy**: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and or large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness have

Class Effects:	Quinolones: Second-Generation
	been reported in patients receiving quinolones. **Neurotoxicity**: risk factors include renal failure, underlying CNS disease, and increased CNS penetration of the drug Patients with seizure history. Patients with myasthenia gravis; may exacerbate symptoms.
Drug Interactions	▪ Decreased GI absorption: sucralfate, iron salts, didanosine, antacids ▪ Theophylline ▪ Cimetidine ▪ Anticoagulants ▪ NSAIDs ▪ Antidiabetic agents ▪ Caffeine Additional drug-specific interactions are listed in the drug monograph.

Drug Class:	Quinolones: Second-Generation			
Characteristic	**ciprofloxacin**	**lomefloxacin**	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Maxaquin®	Noroxin®	Floxin®
Date of FDA Approval	Oct 1987	Feb 1992	Oct 1986	Dec 1990
Generic available?	Yes	No	No	Yes
Manufacturer (if single source)		Searle	Merck	
Dosage forms / route of administration	IR Tablet: 100, 250, 500, 750 mg ER Tablet: 500 mg Suspension: 250 or 500 mg/5mL	Tablet: 400 mg	Tablet: 400 mg	Ophthalmic: 0.3% Otic: 0.3% IV: 200mg/50ml, 400mg/100ml Tablet: 200, 300, 400 mg
Dosing frequency	▪ IR: q 12 h ▪ ER: once daily	Once daily	Q 12 hr	Q 12 hr

Drug Class:	Quinolones: Second-Generation			
Characteristic	**ciprofloxacin**	**lomefloxacin**	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Maxaquin®	Noroxin®	Floxin®
General dosing guidelines (oral)	▪ IR: usually 500 mg q 12h (250-750 q 12h) ▪ ER: 500 mg q 24h (only indicated for acute uncomplicated UTI)	▪ Usual oral adult dose: 400 mg daily for 3 to 14 days, depending on the organism and site of infection. ▪ The dose for prevention of urinary tract infections after transurethral surgery or transrectal prostate biopsies is 400 mg one time, 1 to 6 hours prior to the procedure.	▪ 400 mg q 12 hr - administered at least one hour before or at least two hours after a meal or ingestion of milk and/or other dairy products. ▪ Uncomplicated gonorrhea – 800 mg x one dose	▪ Chronic bronchitis: 400 mg every 12 hr for 10 days ▪ Community-acquired pneumonia: 400 mg every 12 hr for 10 days ▪ Cystitis: (*E. coli, K. pneumoniae)* 200 mg every 12 hr for 3 days ▪ Cystitis: (other approved organisms) 200 mg every 12 hr for 7 days ▪ Gonorrhea: 400 mg as a single dose ▪ Nongonococcal cervicitis/urethritis: 300 mg every 12 hr for 7 days ▪ Pelvic inflammatory disease: 400 mg every 12 hr for 10-14 days ▪ Prostatitis: 300 mg every 12 hr for 6 weeks ▪ Skin/skin structure infection: 400 mg every 12 hr for 10 days ▪ Urinary tract infection, complicated: 200 mg every 12 hr for 10 days
Other Studied Uses	▪ Chancroid ▪ Cholera ▪ Colitis - antibiotic-induced ▪ Crohn's disease	▪ Dermatologic infections ▪ Gonococcal urethritis ▪ Nongonococcal urethritis	▪ Pediatric gastroenteritis ▪ Prophylaxis in neutropenic patients ▪ Malaria	▪ Acute salpingitis ▪ Bacterial infection prophylaxis ▪ Biliary tract infection ▪ Bone and joint infection

Drug Class:	Quinolones: Second-Generation			
Characteristic	**ciprofloxacin**	**lomefloxacin**	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Maxaquin®	Noroxin®	Floxin®
	▪ Cystic fibrosis ▪ Enterococcus UTIs ▪ *H. pylori* - triple therapy ▪ *Mycobacteria* non-tuberculous – combination therapy ▪ *Neisseria meningitidis* ▪ Peritonitis ▪ Plague ▪ Prophylaxis prior to colorectal surgery or biliary tract surgery ▪ *Rickettsia* infections ▪ *Salmonella* infections and carriers ▪ Tularemia ▪ Ulcerative colitis		▪ *Salmonella* ▪ Shigellosis ▪ Travelers' diarrhea prophylaxis ▪ Urinary tract infection prophylaxis	▪ Cholera ▪ Epididymitis ▪ Infectious diarrhea ▪ Leprosy ▪ Pyelonephritis ▪ Q fever ▪ *Salmonella* ▪ Sepsis ▪ *Shigella* infection ▪ Surgical prophylaxis ▪ Typhoid fever
Drug Interactions (drug-specific)	▪ Cyclosporine ▪ Methotrexate ▪ Probenecid	▪ Probenecid	▪ Cyclosporine ▪ Nitrofurantoin ▪ Probenecid	▪ Procainamide ▪ Quinidine ▪ Amiodarone ▪ Sotalol
Pharmacokinetic Issues	Peak serum levels occur in 1 to 1.2 hours following PO doses; ciprofloxacin is metabolized in the liver to active metabolites, and 30% to 57% of a PO dose is recovered unchanged in the urine; the elimination half-life is 3 to 6 hours. Can be taken with food or on an empty stomach. Should not be taken with dairy products (like milk	Lomefloxacin is well-absorbed after oral administration. Lomefloxacin is 20% protein bound. This drug is excreted primarily unchanged in the urine with an elimination half-life ranging from 6.4 to 8.19 hours. Food prolongs the time to Cmax and decreases the peak concentration. Since the extent of	Following a 400 mg dose in healthy volunteers, norfloxacin urinary concentrations remain above 30 mcg/mL for at least 12 hours. Since the MIC of norfloxacin for most bacteria is less than 4 mcg/mL, urinary concentrations of the drug given BID are more than adequate to provide bactericidal activity.	Ofloxacin is well absorbed after oral administration; administration with food causes only minor alterations in absorption. Ofloxacin is 20% to 32% plasma protein bound; the volume of distribution is 2.4 to 3.5 L/kg. Ofloxacin is excreted primarily unchanged in the urine with an elimination half-life of 5 to 7.5

Drug Class:	Quinolones: Second-Generation			
Characteristic	**ciprofloxacin**	**lomefloxacin**	**norfloxacin**	**ofloxacin**
	Cipro®, Cipro XR®	Maxaquin®	Noroxin®	Floxin®
	or yogurt) or calcium-fortified juices alone; however, it may be taken with a meal that contains these products.	absorption is not significantly reduced, this drug may be taken with or without food. 65% of oral dose excreted in the urine.		hours.
Renal Impairment	Dose adjustments should be made as follows: ClCr30-50 mL/min: 250-500 mg q12h ClCr=5-29 ml/min: 250-500 mg q18h	ClCr 10-40 mL/min: initial oral loading dose of 400 mg is followed by 200 mg once daily for the duration of therapy.	ClCr < 30 mL/min/1.73 m^2 : The recommended dose is 400 mg once daily for the same duration as patients with normal renal function.	Adjust the dose as follows: ClCr=20-50 mL/min: usual dose q24h ClCr<20 ml/min: ½ usual dose q24h
Pregnancy	FDA Category C			
	According the CDC, ciprofloxacin is the antibiotic of choice for initial prophylactic therapy for asymptomatic pregnant women exposed to *B. anthracis*. If the isolate is found to be penicillin-susceptible, amoxicillin may be considered to finish the 60-day prophylaxis course.			
Geriatric	No specific geriatric recommendation but dose adjustments should be made for patients with a CrCl =50 mL/min (ciprofloxacin and ofloxacin), CrCl < 40 ml/min for lomefloxacin and CrCl <30 mL/min for norfloxacin.			

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Abstracts

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Lomefloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis.

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A total of 182 patients with chronic bacterial prostatitis (CBP) were recruited into this multicentre prospective, randomized clinical study. Of these, 93 were treated orally with lomefloxacin (LOMX) 400 mg once daily and 89 with ciprofloxacin (CIPX) 500 mg twice daily for 4 weeks. At 5-9 days 90/90 vs 86/86, at 4-6 weeks 82/83 vs 82/82, at 3 months 80/79 vs 78/75, and at 6 months 78/75 vs 75/72 patients aging from 18 to 70 years were evaluable bacteriologically/clinically according to a modified intention to treat evaluation. The most frequent pathogens were *Escherichia coli*, followed by staphylococci, enterococci and *Proteus mirabilis*. At 5-9 days, 4-6 weeks, 3 and 6 months after therapy the rates of eradication without superinfection per evaluable patients (100%) were 80, 72, 74, and 63% in the LOMX group and 84, 81, 82, and 72% in the CIPX group and (cure and improvement) rates were 98 vs 97%, 84 vs 90%, 86 vs 89%, and 81 vs 89%. There were no statistically significant differences ($P < 0.05$) between the results of the two treatment groups. Nine (5 vs 4) patients were withdrawn because of adverse events. From the bacteriological and clinical results including adverse events, the oral treatment of CBP over 4 weeks with LOMX 400 mg once daily was comparably effective and tolerable with that of CIPX 500 mg twice daily.

FABS Lett., 1991; 141 (11):223-27.

Quinolones for uncomplicated acute cystitis in women: A systematic review.

Rafalski V, Andreeva I, Riabkova E.

Urinary tract infections (UTIs) are common with an estimated annual global incidence of at least 250 million cases. Acute cystitis is the most prevalent form of uncomplicated UTIs. Antimicrobials with proven efficacy in acute cystitis are co-trimoxzole, nitrofurantoin, quinolones, and fluoroquinolones. People are diagnosed with acute cystitis are usually treated as outpatients and therefore tolerance and antimicrobial safety needs to be carefully considered. The objectives of this investigation are to 1) Compare the efficacy, safety, and tolerance of different quinolones in patients with acute, uncomplicated cystitis (AUC). 2) Compare different quinolones given as either a single dose, short course (three to seven days) or as a long course (seven to 14 days). The literature search was done using search strategy by electronic database MEDLINE and EMBASE. This was performed independently by two reviewers. Types of interventions were randomized controlled design (RCTs) comparing two or more quinolones. Types of outcome measures were: 1) Clinical response: cure, improvement, failure, recurrence, clinical success, sustained clinical success. 2) Bacteriological response: eradication, persistence, relapse, reinfection, sustained bacteriological success. 3) Overall success. 4) Adverse events: any adverse events, organ or system specific AE, serious adverse events. There were 224 references identified and 40 studies have been selected. Among theses 16 RCT evaluated ciprofloxacin, norfloxacin, ofloxacin, lomefloacin, perfloxacin, rufloxacin, sparfloxacin, temafloxacin in different regimes were included. We have not found two or more RCT compared the same pair of quinolones so we have not performed the data combining. There was no statistically significant difference in clinical and microbiological efficacy between quinolones given in equivalent course. However significant differences in safety among these antimicrobials were found, e.g. photosensitivity frequently occurred when used sparfloxacin as compared to ofloxacin (OR=15.77, p=0.008) and ciprofloxacin (OR=13.14, p=0.01); frequency of any adverse reactions (AE), skin AE and AE require discontinuation of medication when lomefloxacin was compared with norfloxacin (OR=2.06, p=0.01; OR=14.95, p=0.0002 and OR= 7.0, p=0.01.

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A comparative study of the distribution of ofloxacin and ciprofloxacin in prostatic tissues after simultaneous oral ingestion

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Objectives

To determine the levels of two quinolones, ofloxacin and ciprofloxacin, potent broad-spectrum antibiotics with very good oral bioavailability and low minimum inhibitory concentrations (MICs) for most pathogens, in the prostates of patients who underwent transurethral resection of the prostate (TURP) after oral ingestion for surgical prophylaxis.

Patients and Methods

Twenty-eight patients with BPH requiring a TURP ingested 250 mg of both drugs 2-4 h before operation. The levels of the drugs in the serum and prostate were measured using high-performance liquid chromatography and the levels of both drugs determined at the 6 and 9 o'clock positions in the prostate to examine any local variations in drug concentration.

Results

Ofloxacin concentrations were significantly higher in the serum and prostatic tissues compared with ciprofloxacin for the same dose, but its penetrance into the prostate was lower. This mainly reflected its higher oral bioavailability. Both drugs were present in concentrations 50% higher at the 6 o'clock than at the 9 o'clock position but both exceeded the MICs for most Gram-negative organisms except *Pseudomonas*.

Conclusion

Ofloxacin has the advantage against ciprofloxacin of exceeding the MICs for *Staphylococcus* and *Chlamydia*. However, ciprofloxacin has the advantage of having prostate-to-serum ratios of unity, but for the same dose the prostatic concentrations of ofloxacin is significantly higher.

Drug Class:	Quinolones: Third-Generation		
Drugs Reviewed:	gatifloxacin (Tequin®)	levofloxacin (Levaquin®)	moxifloxacin (Avelox®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

There are currently four third-generation quinolones available in the United States for general use as indicated above. Trovafloxacin (Trovan®), a fourth generation quinolone, was associated with serious liver injury resulting in liver transplantation or death and has been discontinued by the manufacturer. Sparfloxacin (Zagam®) was withdrawn from market due to commercial reasons in 2001.

- The fluoroquinolones are effective in treating both gram-positive and gram-negative infections.
- There is no clinical evidence to suggest greater efficacy of any one of the third-generation quinolones (gatifloxacin, levofloxacin, or moxifloxacin) over another one for the vast majority of respiratory tract infections.

Efficacy

Gram positive organisms: As a class, the third generation quinolones (Avelox®, Tequin® and Levaquin®) have superior activity against *S.pneumoniae* in comparison to Cipro®, Noroxin®, Floxin®, and Maxaquin®. The second generation quinolones have activity against S. aureus (Methicillin sensitive), but the newer third generation agents appear to be more potent.

Gram Negative: Ciprofloxacin has been accepted as the most active against Pseudomonas aeruginosa and is capable of reaching concentrations high enough for use in systemic pseudomonal infections. Other second generation quinolones are not recommended for use in systemic pseudomonal infections, but may be used in the treatment of urinary tract infections of *Pseudomonas aeruginosa* where higher concentrations of the drug can be reached. Recent in vitro evidence suggests that the third generation fluoroquinolones, levofloxacin (Levaquin®) and gatifloxacin (Tequin®), are as active against P. aeruginosa as ciprofloxacin.

Atypical organisms: All quinolones (minus the first generation) have coverage against atypicals such as Mycoplasma, Chlamydia, and Legionella. For the treatment of atypical pneumonias, macrolides are likely to be equivalent to fluoroquinolones and are currently more cost-effective. Quinolones provide exceptional coverage against atypical pathogens when infection with these organisms is suspected in patients with community-acquired pneumonia. However, ofloxacin has been associated with treatment failures, and ciprofloxacin has displayed reduced activity against Chlamydia species.

Adverse Events

Gastrointestinal adverse events (ranked from highest to lowest): Moxifloxacin (Avelox®) > Gatifloxacin (Tequin®) > Ciprofloxacin (Cipro®) > Norfloxacin (Noroxin®) > Ofloxacin (Floxin®) > Levofloxacin (Levaquin®)

CNS adverse events (ranked from highest to lowest): Norfloxacin (Noroxin®), Gatifloxacin (Tequin®) > Moxifloxacin (Avelox®) > Ciprofloxacin (Cipro®) > Ofloxacin (Floxin®) > Levofloxacin (Levaquin®)

Dermatologic/Phototoxicity: Gatifloxacin (Tequin®), moxifloxacin (Avelox®) and levofloxacin (Levaquin®) appear to have the lowest potential for inducing phototoxicty.

QT prolongation: Levofloxacin, moxifloxacin, and gatifloxacin have all been associated with QTc prolongation. Several authors have suggested the risk of QTc prolongation and torsades de pointes is small,

and can be minimized by avoiding use in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA or class III antiarrhythmics.

Blood glucose should be closely monitored in patients with diabetes taking quinolones. Changes in blood glucose (symptomatic hyper- and hypoglycemia) in patients on concurrent oral hypoglycemic or insulin therapy.

Tendon and Cartilage Effects: Fluoroquinolones as a class have been shown to cause tendon ruptures of shoulder and or Achilles tendons. Post-marketing surveillance reports indicate risk may be increased in patients receiving concomitant corticosteroids. Discontinue therapy if the patient experiences pain, inflammation, or rupture of a tendon.

Unique Features

- Levofloxacin: Levofloxacin is the l-isomer of ofloxacin. In comparison to ofloxacin, levofloxacin has fewer CNS side effects, a longer half-life (once daily dosing), extended spectrum of activity, and twice the potency. For most bacteria, the MIC values for levofloxacin are half those of ofloxacin. There have been case reports of levofloxacin failure in patients with pneumococcal respiratory tract infections.
- Factive (gemifloxacin) is a fourth generation fluoroquinolone. It is a fluoronaphthyridone carboxylic acid with a pyrrolidine substituent; these changes confer enhanced activity against gram-positive pathogens without significantly compromising gram-negative activity. It is only available as an oral tablet and is indicated for the treatment of chronic bronchitis and community-acquired pneumonia. Hepatic metabolism is limited, with no important p450 enzyme involvement. Gemifloxacin shares the class warning and contraindications of the third generation agents. Gemifloxacin has the potential for QT prolongation in some patients, especially those with a history of QT prolongation, hypokalemia or hypomagnesemia, and those receiving class IA or III antiarrhythmic agents. No studies have been performed. The most common adverse effects included diarrhea, rash, nausea, and headache. Low propensity for photosensitivity.

Summary of Indications (oral formulations)

gatifloxacin	levofloxacin	moxifloxacin
Tequin®	Levaquin®	Avelox®
▪ Acute exacerbations of chronic bronchitis ▪ Cystitis ▪ Gonorrhea – uncomplicated rectal (women), urethral and cervical ▪ Pyelonephritis ▪ Sinusitis ▪ Skin & skin structure infections, uncomplicated ▪ Urinary tract infections ▪ Community-acquired pneumonia	▪ Acute exacerbations of chronic bronchitis ▪ Chronic prostatitis ▪ Community-acquired pneumonia ▪ Nosocomial pneumonia ▪ Sinusitis ▪ Skin and skin structure infections – complicated and uncomplicated ▪ Urinary tract infections ▪ Pyelonephritis	▪ Acute exacerbations of chronic bronchitis ▪ Community-acquired pneumonia ▪ Sinusitis ▪ Skin and skin structure infections, uncomplicated

Place in Therapy

Respiratory Tract Infections: Because of concerns regarding emerging resistance, fluoroquinolones with antipneumococcal activity should be reserved as second-line agents in the treatment of community-acquired pneumonia. According to a report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group (Heffelfinger et al, 2000), the use of fluoroquinolones in community-acquired pneumonia should be limited to adults under the following circumstances:

- Patients in which initial therapy with a suitable empirical antipneumococcal agent has failed.
- Patients who are allergic to suitable alternative agents.
- Patients who have a documented infection with a highly resistant pneumococci; penicillin MIC greater = to 4 µg/mL.

Ofloxacin has been effective in the treatment of respiratory tract infections. Acute bronchitis is generally due to pneumococci and ofloxacin will not replace beta-lactam antibiotics as drug of first choice in these cases. However, ofloxacin and other quinolones may be useful in the treatment of bronchitis due to gram-negative organisms when beta-lactams or erythromycin have failed. Beta-lactams, macrolides, or cotrimoxazole (sulfamethoxazole and trimethoprim) will continue to be drugs of first choice for community-acquired pneumonia; however, ofloxacin and other quinolones may become initial therapy for hospital-acquired gram-positive pneumonia.

Urinary Tract Infections: Cotrimoxazole is the recommended standard therapy for uncomplicated urinary tract infections in women. Trimethoprim and fluoroquinolones have similar efficacy. Fluoroquinolones are not recommended as initial empirical therapy due to issues of cost, as well as restricting use to prevent the development of resistance. Fluoroquinolones may be considered in communities with high rates (greater than 10% to 20%) of cotrimoxazole resistance.

Prostatitis: Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue. When taken for four to six weeks, norfloxacin, ciprofloxacin, levofloxacin, and ofloxacin have eradication rates of 67 to 91 percent, irrespective of antibiotic. Ciprofloxacin should be reserved for use in patients with resistant gram-negative, pseudomonal prostatitis because of its superior activity against P. aeruginosa.

Acute sinusitis: The FDA has labeled ciprofloxacin (Cipro®), gatifloxacin (Tequin®), moxifloxacin (Avelox®), and levofloxacin (Levaquin®) for use in the treatment of acute bacterial sinusitis. Clinical trials comparing fluoroquinolones with amoxicillin-clavulanate potassium (Augmentin®), cefuroxime axetil (Ceftin®), and clarithromycin (Biaxin®) have demonstrated the efficacy of the quinolone antibiotics. Generally quinolones are considered second line agents in the treatment of acute sinusitis.

Sexually Transmitted Diseases (Based on 2002 CDC guidelines): Ofloxacin 400 mg po single dose or levofloxacin 250 mg PO single dose are considered drugs of choice for uncomplicated gonococcal infections, while gatifloxacin 400 mg PO single dose or lomefloxacin 400 mg PO single dose are considered alternative therapy. In the treatment of chlamydial infections, ofloxacin 300 mg PO bid x 7 days or levofloxacin 500 mg PO qd x 7 days are considered alternative therapy. In the treatment of epididymitis, ofloxacin 300 mg PO bid or levofloxacin 500 mg PO qd are considered alternative therapy.

Gonorrhea: Quinolone-resistant N. gonorrhoeae is a continuing problem. Quinolone antibiotics should not be used for infections acquired in Asia or the Pacific (including Hawaii), and use for infections acquired in California may be inadvisable; surveillance for antimicrobial resistance is important for guiding therapy recommendations in the treatment of N. gonorrhoeae (CDC, 2002).

Department of Veterans Affairs Formulary

- Ciprofloxacin (2nd)
- Gatifloxacin (3rd)

Summary of Pipeline Agents Expected to Offer Related Treatment Options

Garenoxacin (Toyama Chemical/Schering-Plough) - des-fluoroquinolone antibiotic for treatment of respiratory infections, including chronic bronchitis, community-acquired pneumonia and acute maxillary sinusitis; once-daily oral and intravenous formulations. Phase III complete; NDA submission planned for late 2005 (as of 6/2004).

Levofloxacin oral solution formulation - NDA Submitted 12/2003 - Estimated User Fee Goal 10/2004

Prulifloxacin (Optimer Pharmaceuticals) - fluoroquinolone antibiotic with activity against gram-positive and gram-negative organisms for treatment of community-acquired respiratory tract infections and urinary tract infections. Phase III (as of 2004); NDA submission predicted for 4Q:05 (as of 2004).

Class Effects:	Quinolones: Third-Generation
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Quinolones affect bacterial cells by interfering with DNA and the enzyme DNA gyrase and topoisomerase IV. The formation of the quinolone-gyrase-DNA complex prevents the DNA polymerase from proceeding at the replication fork, thus stopping DNA synthesis.
Pediatric Labeling	Safety and efficacy has not been established in children under 18 years old.
Contraindications	▪ Hypersensitivity to any fluoroquinolones
Major Adverse Effects / Warnings	▪ GI, CNS most common adverse events; mild, may resolve with continued treatment ▪ Neurotoxicity; risk factors include renal failure, underlying CNS disease, and increased CNS penetration of the drug ▪ Tendonitis/tendon rupture: risk factors include patients over 60 years of age, renal failure, dialysis, concomitant corticosteroid therapy, and dyslipidemia ▪ Arthopathy ▪ Patients with seizure history ▪ QT prolongation ▪ Changes in blood glucose, in diabetics treated with concomitant hypoglycemic therapy ▪ Antibiotic associated pseudomembranous colitis ▪ Phototoxicity ▪ Patients with myasthenia gravis; may exacerbate symptoms ▪ Patients with glucose 6-phosphate dehydrogenase deficiency; may induce rare hemolytic reactions
Drug Interactions	▪ Decreased GI absorption: sucralfate, iron salts, didanosine, antacids ▪ NSAIDs – increased risk of CNS stimulation (not observed in clinical trials with gatifloxacin or moxifloxacin) ▪ Antiarrhythmic agents Additional drug-specific interactions are listed in the drug monograph.

Drug Class:	Quinolones: Third-Generation		
Characteristic	**gatifloxacin** Tequin®	**Levofloxacin** Levaquin®	**Moxifloxacin** Avelox®
Structure-Activity	Gatifloxacin is a 6-fluoro-8-methoxy quinolone	Ofloxacin exists as 2 optically-active isomers. Levofloxacin is the S(-)-enantiomer of ofloxacin, and is considered primarily responsible for the clinical antibacterial efficacy of the racemate. It is reportedly 8 to 128 times more potent than R(+)-ofloxacin and twice as potent as racemic ofloxacin.	Moxifloxacin differs from other quinolones in that is has a methoxy function at the 8-position, and an S,S – configured diazabicyclononyl ring moiety at the 7 position. The methoxy group contributes to a unique set of pharmacokinetic and pharmacodynamic characteristics
Spectrum	▪ Gatifloxacin is a fluoroquinolone with expanded activity against gram-positive organisms. In general, the in vitro activity of gatifloxacin is similar to or greater than that of other fluoroquinolones in clinical use against gram-positive and fastidious species. ▪ Against anaerobes, gatifloxacin is more active than ciprofloxacin and ofloxacin, as active as tosufloxacin and sparfloxacin, and less active than trovafloxacin.	▪ Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections: Aerobic gram-positive microorganism: *Enterococcus faecalis, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes.* Aerobic gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa*. ▪ Levofloxacin is active against most of the organisms responsible for bacterial gastroenteritis such as *Salmonella* species, *Shigella* species, *Yersinia enterocolitica, Campylobacter jejuni*, and *E. coli*.	▪ Moxifloxacin is a fluoroquinolone with a broad spectrum of antimicrobial activity, including gram-positive and gram-negative organisms, *Chlamydia* spp, anaerobes, and *Mycobacterium tuberculosis*. Similar to trovafloxacin, grepafloxacin, and sparfloxacin, the activity of moxifloxacin against gram-positive pathogens is improved relative to conventional fluoroquinolones. ▪ There is some in vitro evidence that resistance to moxifloxacin in gram-positive bacteria occurs more slowly and is less frequent compared to other fluoroquinolones, including trovafloxacin and grepafloxacin.
Date of FDA Approval	Dec 1999	Dec 1996	Dec 1999
Generic available?	No	No	No
Manufacturer (if single source)	Bristol-Myers Squibb	Ortho McNeil	Bayer

Drug Class:	Quinolones: Third-Generation		
Characteristic	**gatifloxacin** Tequin®	**Levofloxacin** Levaquin®	**Moxifloxacin** Avelox®
Dosage forms / route of administration	**Tablet**: 200 mg , 400 mg **Suspension**: 200 mg/5 ml **Injection**: 10mg/ml, 2 mg/ml	**Tablet**: 250 mg, 500 mg, 750 mg **Injection**: 25 mg/ml	**Tablet**: 400 mg **Injection**: 400 mg/250 ml
Dosing frequency	Once daily		
General dosing guidelines	400 mg daily	▪ Most indications: 500 mg every 24 hours for 7 to 14 days, depending on the indication. ▪ Complicated skin and skin structure infections and nosocomial pneumonia: 750 mg every 24 hours. ▪ UTI: 250 mg every 24 hours for 3 days (uncomplicated) and 10 days (complicated).	▪ Respiratory tract infections (including sinusitis, chronic bronchitis, and CAP):, 400 mg once daily for 5 to 10 days. ▪ Uncomplicated skin and skin structure infections: 400 mg once daily for 7 days.
Other Studied Uses	▪ Tuberculosis ▪ Otitis Media	▪ Enteritis ▪ Gynecological infections ▪ Infectious diarrhea ▪ Otitis ▪ Chlamydia ▪ Cervical, urethral, and rectal gonorrhea ▪ Pelvic inflammatory disease ▪ Tuberculosis	▪ Tuberculosis
Major Adverse Events/Warnings (besides class effects)	▪ Gatifloxacin has been well tolerated. The most common adverse effects include nausea, diarrhea, headache, dizziness, and vaginitis. ▪ Gatifloxacin appears to have a low propensity for phototoxicity or crystalluria. ▪ Potential for QT prolongation in some patients, especially those with a history of QT prolongation, hypokalemia or hypomagnesemia, and those receiving class IA or III antiarrhythmic agents.	▪ Common side-effects of the oral and intravenous dosage forms include nausea, headache, diarrhea, insomnia, dizziness, and constipation. ▪ Levofloxacin should be avoided in patients with prolongation of the QT interval.	▪ Nausea and diarrhea are the most common adverse effects of oral therapy. ▪ Moxifloxacin should be avoided in patients with prolongation of the QT interval.

Drug Class:	Quinolones: Third-Generation		
Characteristic	**gatifloxacin** Tequin®	**Levofloxacin** Levaquin®	**Moxifloxacin** Avelox®
Drug Interactions (drug-specific)	Probenecid	▪ Cimetidine – increased AUC but no dosage adjustments required ▪ Anticoagulants – no significant effects on PK parameters noted, however there are post-marketing reports that levofloxacin enhances the effects of warfarin ▪ Probenecid	
Pharmacokinetic Issues	▪ Rapidly absorbed, with peak serum levels occurring in 1-2 hours. Metabolism is minimal and the majority of a dose is excreted unchanged in the urine. ▪ The elimination half-life ranges from 7-14 hours. ▪ Because of similar pharmacokinetics, the oral and intravenous routes of administration are considered interchangeable. ▪ Can be given concurrently with food, including milk and dietary supplements containing calcium. Oral doses of gatifloxacin should be given at least 4 hrs before ferrous sulfate, dietary supplements containing zinc, magnesium, or iron, or antacids containing magnesium or aluminum.	▪ Levofloxacin is essentially completely absorbed after oral administration with peak plasma concentrations attained 1 to 2 hours after the dose. ▪ Levofloxacin does not invert metabolically to its enantiomer, D-ofloxacin, and is excreted primarily unchanged in the urine. ▪ The elimination half-life of levofloxacin is 6 to 8 hours. ▪ Oral levofloxacin can be taken without regard to meals. Oral doses of levofloxacin should be given at least 2 hrs before or 2 hrs after ferrous sulfate, dietary supplements containing zinc, magnesium, or iron, or antacids containing magnesium or aluminum.	▪ The oral bioavailability of moxifloxacin is approximately 90%; after usual therapeutic doses (400 mg), peak plasma levels occur in 1.5 hours. ▪ Moxifloxacin is metabolized in the liver and excreted in urine (20% unchanged) and bile; metabolites do not appear active. The elimination half-life of moxifloxacin is about 13 hours. ▪ Moxifloxacin may be administered without regard to meals. Oral doses should be given at least 4 hrs before or 8 hrs after ferrous sulfate, dietary supplements containing zinc, magnesium, or iron, or antacids containing magnesium or aluminum.
Renal Impairment	Since the majority of a dose is excreted unchanged in the urine, a dosage adjustment is recommended for patients with a ClCr < 40 mL/min, including patients on hemodialysis and on CAPD. The recommended dosage in patients with renal impairment is an initial dose of 400	To avoid drug accumulation, dosage adjustments are necessary in patients with ClCr <50 mL/min. In the treatment of acute bacterial exacerbation, chronic bronchitis, community acquired pneumonia, acute maxillary sinusitis,	No dosage adjustment is required based on renal function.

Drug Class:	Quinolones: Third-Generation		
Characteristic	**gatifloxacin**	**Levofloxacin**	**Moxifloxacin**
	Tequin®	Levaquin®	Avelox®
	mg followed by: ➢ ClCr =40 mL/min: 400 mg every day ➢ ClCr<40 mL/min: 200 mg every day ➢ Hemodialysis: 200 mg every day ➢ CAPD: 200 mg every day	chronic prostatitis, uncomplicated skin and skin structure infection, the recommended dosage for patients with impaired renal function is a initial dose of 500 mg followed by: ➢ ClCr 20-49 ml/min: 250 mg every 24 hours ➢ ClCr 10-19 ml/min: 250 mg every 48 hours ➢ Hemodialysis: 250 mg every 48 hours ➢ CAPD: 250 mg every 48 hours	
Hepatic impairment	No dosage adjustment is necessary in patients with moderate hepatic impairment. There are no data in patients with severe hepatic impairment.	Due to the limited extent of levofloxacin metabolism, the pharmacokinetics are not expected to be affected by hepatic impairment.	No dosage adjustment is necessary in patients with moderate hepatic impairment. There are no data in patients with severe hepatic impairment.
Geriatric	No dosage adjustment required based on age alone or on gender.		

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Abstracts

Chemotherapy. 2004 Apr;50(1):40-2.

Comparative in vitro activities of three new quinolones and azithromycin against aerobic pathogens causing respiratory tract and abdominal wound infections.

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BACKGROUND: In our study the in vitro susceptibility of common pathogens that cause respiratory tract and abdominal wound infections was tested against two newer fluorquinolones (moxifloxacin and gatifloxacin) as well as levofloxacin and azithromycin. METHODS: 50 isolates each of methicillin-susceptible Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa and Haemophilus influenzae isolated from the respiratory tract and from wounds were tested for their susceptibility to moxifloxacin, gatifloxacin, levofloxacin and azithromycin. RESULTS: Moxifloxacin proved to be the most active substance against the tested gram-positive pathogens. Gatifloxacin was the most active against P. aeruginosa. Moxifloxacin and gatifloxacin proved to be comparably active against the clinical isolates of E. coli and H. influenzae. CONCLUSIONS: Moxifloxacin and gatifloxacin display

excellent activity against respiratory pathogens as well as nosocomial pathogens causing abdominal wound infections. When treating infections caused by P. aeruginosa the earlier fluorquinolones such as ciprofloxacin or ofloxacin are the substances of choice.

Clin Infect Dis. 2003 Nov 1;37(9):1210-5. Epub 2003 Oct 02.

Gatifloxacin, gemifloxacin, and moxifloxacin: the role of 3 newer fluoroquinolones.

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Gatifloxacin, gemifloxacin, and moxifloxacin are the newest fluoroquinolones and show excellent in vitro activity against a wide variety of respiratory tract pathogens, many gram-negative aerobic organisms, and Bacteroides fragilis. These agents may be administered as oral and/or intravenous formulations with excellent bioavailability. The pharmacodynamics of these 3 new fluoroquinolones is more favorable than that of levofloxacin or ciprofloxacin for Streptococcus pneumoniae. All 3 agents are approved for the treatment of acute exacerbation of chronic bronchitis and community-acquired pneumonia. In addition, gatifloxacin and moxifloxacin are approved for the treatment of sinusitis. The toxicity of these 3 agents appears to be similar to that of the other fluoroquinolones in terms of gastrointestinal and central nervous system disturbances. All 3 agents have a low risk of phototoxicity, but gemifloxacin is associated with an increased risk of skin rash that is not a photoreaction. These agents can be useful for treatment of bacterial respiratory tract infections in patients who are allergic to beta-lactams, but caution must be exercised to avoid the potential for selection of widespread resistance, which may occur with indiscriminate use.

Diagn Microbiol Infect Dis. 2000 Jun;37(2):139-42.

Antimicrobial activity of advanced-spectrum fluoroquinolones tested against more than 2000 contemporary bacterial isolates of species causing community-acquired respiratory tract infections in the United States (1999). *

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In vitro activity of four newer fluoroquinolones (clinafloxacin, gemifloxacin, moxifloxacin, sitafloxacin) and an equal number control drugs in the same class (ciprofloxacin, grepafloxacin, levofloxacin, trovafloxacin) was determined by reference dilution tests against 2156 recent United States clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. All the fluoroquinolones demonstrated excellent in vitro activity against these pathogens. Streptococcus pneumoniae isolates were fully susceptible to clinafloxacin, sitafloxacin, and gemifloxacin at 0.5 microg/ml, and over 98% of sampled strains had MICs of </=1 microg/ml for grepafloxacin, moxifloxacin and trovafloxacin. Penicillin resistance did not influence the potency of the tested fluoroquinolones. All the isolates of H. influenzae and M. catarrhalis were inhibited by the investigational, as well as comparator fluoroquinolones at </=0.5 microg/ml, irrespective of their beta-lactamase producing abilities. In conclusion, the investigational fluoroquinolones demonstrated excellent activity against these major respiratory tract pathogens isolated in 1999, and some remain safe candidates for empiric therapy of community-acquired respiratory tract infections and selected infections in hospitalized patients.

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Comparison of the in vitro activities of several new fluoroquinolones against respiratory pathogens and their abilities to select fluoroquinolone resistance.

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In this study the in vitro activities and pharmacodynamic properties of moxifloxacin, levofloxacin, gatifloxacin and gemifloxacin were compared on recently isolated respiratory pathogens and strains of Streptococcus pneumoniae with known mechanisms of fluoroquinolone resistance. In addition, the resistance selection frequencies of moxifloxacin and levofloxacin on three recently isolated respiratory pathogens and four strains of S. pneumoniae with known mechanisms of fluoroquinolone resistance were investigated. The four fluoroquinolones had similar activities against both Moraxella catarrhalis (MIC(90)s 0.015-0.06 mg/L) and Haemophilus influenzae (MIC(90)s 0.008-0.03 mg/L). More marked differences in activity were noted with S. pneumoniae, with MIC(90)s of 0.25, 1, 0.5 and 0.03 mg/L for moxifloxacin, levofloxacin, gatifloxacin and gemifloxacin, respectively. With the S. pneumoniae strains, the four fluoroquinolones exhibited similar concentration-dependent time-kill kinetics. The resistance selection frequencies of levofloxacin were higher than those of moxifloxacin at concentrations equivalent to those at the end of the dosing interval. Therefore moxifloxacin may have less of an impact on the development of resistance than levofloxacin.

Antimicrob Agents Chemother. 2001 Jun;45(6):1721-9.

Antimicrobial resistance among clinical isolates of Streptococcus pneumoniae in the United States during 1999--2000, including a comparison of resistance rates since 1994--1995. *

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A total of 1,531 recent clinical isolates of Streptococcus pneumoniae were collected from 33 medical centers nationwide during the winter of 1999--2000 and characterized at a central laboratory. Of these isolates, 34.2% were penicillin nonsusceptible (MIC > or = 0.12 microg/ml) and 21.5% were high-level resistant (MIC > or = 2 microg/ml). MICs to all beta-lactam antimicrobials increased as penicillin MICs increased. Resistance rates among non-beta-lactam agents were the following: macrolides, 25.2 to 25.7%; clindamycin, 8.9%; tetracycline, 16.3%; chloramphenicol, 8.3%; and trimethoprim-sulfamethoxazole (TMP-SMX), 30.3%. Resistance to non-beta-lactam agents was higher among penicillin-resistant strains than penicillin-susceptible strains; 22.4% of S. pneumoniae were multiresistant. Resistance to vancomycin and quinupristin-dalfopristin was not detected. Resistance to rifampin was 0.1%. Testing of seven fluoroquinolones resulted in the following rank order of in vitro activity: gemifloxacin > sitafloxacin > moxifloxacin > gatifloxacin > levofloxacin = ciprofloxacin > ofloxacin. For 1.4% of strains, ciprofloxacin MICs were > or = 4 microg/ml. The MIC(90)s (MICs at which 90% of isolates were inhibited) of two ketolides were 0.06 microg/ml (ABT773) and 0.12 microg/ml (telithromycin). The MIC(90) of linezolid was 2 microg/ml. Overall, antimicrobial resistance was highest among middle ear fluid and sinus isolates of S. pneumoniae; lowest resistance rates were noted with isolates from cerebrospinal fluid and blood. Resistant isolates were most often recovered from children 0 to 5 years of age and from patients in the southeastern United States. This study represents a continuation of two previous national studies, one in 1994--1995 and the other in 1997--1998. Resistance rates with S. pneumoniae have increased markedly in the United States during the past 5 years. Increases in resistance from 1994--1995 to 1999--2000 for selected antimicrobial agents were as follows: penicillin, 10.6%; erythromycin, 16.1%; tetracycline, 9.0%; TMP-SMX, 9.1%; and chloramphenicol, 4.0%, the increase in multiresistance was 13.3%. Despite awareness and prevention efforts, antimicrobial resistance with S. pneumoniae continues to increase in the United States.

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Drugs. 2003;63(24):2769-802.

Levofloxacin: a review of its use in the treatment of bacterial infections in the United States.

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Levofloxacin (Levaquin) is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens. It is active against both penicillin-susceptible and penicillin-resistant Streptococcus pneumoniae. The prevalence of S. pneumoniae resistance to levofloxacin is <1% overall in the US.A number of randomised comparative trials in the US have demonstrated the efficacy of levofloxacin in the treatment of infections of the respiratory tract, genitourinary tract, skin and skin structures. Sequential intravenous to oral levofloxacin 750mg once daily for 7-14 days was as effective in the treatment of nosocomial pneumonia as intravenous imipenem/cilastatin 500-1000mg every 6-8 hours followed by oral ciprofloxacin 750mg twice daily in one study. In patients with mild to severe community-acquired pneumonia (CAP), intravenous and/or oral levofloxacin 500mg once daily for 7-14 days achieved clinical and bacteriological response rates similar to those with comparator agents, including amoxicillin/clavulanic acid, clarithromycin, azithromycin, ceftriaxone and/or cefuroxime axetil and gatifloxacin. A recent study indicates that intravenous or oral levofloxacin 750mg once daily for 5 days is as effective as 500mg once daily for 10 days, in the treatment of mild to severe CAP. Exacerbations of chronic bronchitis and acute maxillary sinusitis respond well to treatment with oral levofloxacin 500mg once daily for 7 and 10-14 days, respectively.Oral levofloxacin was as effective as ofloxacin in uncomplicated urinary tract infections and ciprofloxacin or lomefloxacin in complicated urinary tract infections. In men with chronic bacterial prostatitis treated for 28 days, oral levofloxacin 500mg once daily achieved similar clinical and bacteriological response rates to oral ciprofloxacin 500mg twice daily. Uncomplicated skin infections responded well to oral levofloxacin 500mg once daily for 7-10 days, while in complicated skin infections intravenous and/or oral levofloxacin 750mg for 7-14 days was at least as effective as intravenous ticarcillin/clavulanic acid (+/- switch to oral amoxicillin/clavulanic acid) administered for the same duration.Levofloxacin is generally well tolerated, with the most frequently reported adverse events being nausea and diarrhoea; in comparison with some other quinolones it has a low photosensitising potential and clinically significant cardiac and hepatic adverse events are rare. CONCLUSION: Levofloxacin is a broad-spectrum antibacterial agent with activity against a range of Gram-positive and Gram-negative bacteria and atypical organisms. It provides clinical and bacteriological efficacy in a range of infections, including those caused by both penicillin-susceptible and -resistant strains of S. pneumoniae. Levofloxacin is well tolerated, and is associated with few of the phototoxic, cardiac or hepatic adverse events seen with some other quinolones. It also has a pharmacokinetic profile that is compatible with once-daily administration and allows for sequential intravenous to oral therapy. The recent approvals in the US for use in the treatment of nosocomial pneumonia and chronic bacterial prostatitis, and the introduction of a short-course, high-dose regimen for use in CAP, further extend the role of levofloxacin in treating bacterial infections.

Int J Antimicrob Agents. 2000 Nov;16(3):239-43.

In vitro activity of gatifloxacin compared with gemifloxacin, moxifloxacin, trovafloxacin, ciprofloxacin and ofloxacin against uropathogens cultured from patients with complicated urinary tract infections.

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Minimum inhibitory concentrations (MICs) of gatifloxacin were compared with those of gemifloxacin, moxifloxacin, trovafloxacin, ciprofloxacin and ofloxacin using an agar dilution method for 400 uropathogens cultured from the urine of urological patients with complicated and/or hospital-acquired urinary tract infections (UTI). The collection of strains was made up of Enterobacteriaceae (34.5%), enterococci (31.5%), staphylococci (21.2%) and non-fermenting bacteria (12.8%). The antibacterial activity of the three newer fluoroquinolones, gatifloxacin, gemifloxacin, and moxifloxacin, were similar, but showed some drug specific differences. Gemifloxacin was most active against Escherichia coli, but less so against Proteus mirabilis. In this series all isolates of E. coli were inhibited at a MIC of 0.25 mg/l gatifloxacin and moxifloxacin and by 0.125 mg/l gemifloxacin. The MIC distribution of all fluoroquinolones showed a bimodal distribution for staphylococci, enterococci and Pseudomonas aeruginosa. The two modes for P. aeruginosa were 1 and 64 mg/l for gemifloxacin and moxifloxacin and 0.5 and 64 mg/l for gatifloxacin. For staphylococci the two modes were 0.125 and 2 mg/l for gatifloxacin, 0.03 and 4 mg/l for gemifloxacin, and 0.03 and 2 mg/l for moxifloxacin; for enterococci, 0.25 and 16 mg/l for gatifloxacin, 0.06 and 2 mg/l for gemifloxacin, and 0.25 and 8 mg/l for moxifloxacin. Compared with trovafloxacin the MICs were similar, but the newer fluoroquinolones were more active than ciprofloxacin and ofloxacin against Gram-positive bacteria. Of the newer fluoroquinolones gatifloxacin had the highest rate of renal excretion and could be considered a promising alternative fluoroquinolone agent for the treatment of UTI.

Drug Class:	**Macrolides**		
Drugs Reviewed:	Erythromycin Base Erythromycin Estolate Erythromycin Stearate Erythromycin Ethylsuccinate	Clarithromycin (Biaxin®, Biaxin XL®)	Azithromycin (Zithromax®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently three macrolides available in the United States as indicated above - Dynabac (dirithromycin) has been discontinued and is not currently available. The primary differences between them are pharmacokinetics, tolerability and tissue penetration.
- They are all equally efficacious for the treatment of most community acquired infections but clarithromycin and azithromycin have better tolerability and allow BID or QD dosing. Although dirithromycin was dosed once-daily dosing, it offered few other advantages over erythromycin.
- Although higher tissue levels of the newer macrolides may be advantageous for certain infections, there may also be a disadvantage of the low serum levels achieved with these agents. Some infections, such as pneumonia, which can benefit from high tissue levels, may also occur in the presence of a septicemia, and corresponding serum levels may not be adequate for the eradication of the infecting pathogen. Conversely, better tissue penetration has not been demonstrated to improve clinical outcomes compared to conventional therapy with erythromycin base in available clinical trials, including patients with bronchitis, tonsillitis, and skin infections.

Erythromycin is an effective antimicrobial for infections caused by most of the gram-positive bacteria, with limited usefulness in staphylococcal and gram-negative infections. Resistance to erythromycin is commonly reported with hospital-acquired Staph, therefore, sensitivity testing is recommended prior to initiation of erythromycin therapy in this setting.

The unfavorable pharmacokinetic profile (incomplete and unreliable absorption) of oral erythromycin frequently prevents it from being the drug of first choice, in favor of the new macrolides. Abdominal cramping, nausea, and vomiting are commonly reported with cholestatic jaundice, hepatitis, ototoxicity, and hypersensitivity reported less frequently

Azithromycin has several distinct advantages over erythromycin: it is better tolerated; there is better tissue penetration; and there are favorable pharmacokinetics. Azithromycin is dosed once daily which improves patient compliance, an important factor in antibiotic treatment failures. The in-vitro spectrum of activity indicates that azithromycin is slightly less active against most gram-positive organisms than erythromycin, but this is unlikely to be clinically significant. With respect to gram-negative organisms, there is broader activity with azithromycin. Azithromycin has increased susceptibility against *Haemophilus influenzae, Haemophilus parainfluenza, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae, Campylobacter jejuni, Ureaplasma urealyticum, and Neisseria gonorrhoeae*. An advantage with azithromycin is its activity against *Chlamydia trachomatis* and proven efficacy when administered as a single 1 gram dose. The short duration of treatment used, once daily dosing and the acceptable taste to most children make azithromycin a good first choice or alternative agent for many pediatric infections.

Clarithromycin's pharmacokinetic profile has been shown to be superior to erythromycin. Its prolonged elimination half-life after oral dosing allows for twice-daily dosing. In addition, the incidence of side effects, primarily gastrointestinal, is less with clarithromycin than with erythromycin.

Other newer macrolides, clarithromycin and azithromycin in particular, appear to offer more potential than dirithromycin due to greater antimicrobial activity (e.g., *H influenzae* and *C trachomatis* for azithromycin, *L pneumophila* and C *trachomatis* for clarithromycin) and potentially fewer adverse effects; azithromycin can also be given once daily.

Summary of Indications

Erythromycin	Azithromycin	Clarithromycin
	Zithromax®	Biaxin ®, Biaxin XL®
Acne vulgaris (topical) Amebiasis Bacterial endocarditis prophylaxis in penicillin-allergic patients Chlamydia infections Conjunctivitis of the newborn Diptheria Erythrasma Haemophilus influenzae infections Legionnaires' disease Listeriosis Mycoplasma pneumonia Nongonococcal urethritis Otitis media Pelvic inflammatory disease Pertussis Pneumonia of infancy Respiratory infections , upper and lower Rheumatic fever prophylaxis Skin and soft tissue infections Syphilis Uncomplicated urethral, endocervical or rectal infections Urethritis Urethral, endocervical, or rectal infections (caused by *Chlamydia trachomatis*; when tetracyclines are contraindicated) Urogenital infections during pregnancy	Acute bacterial exacerbations chronic obstructive pulmonary disease Acute bacterial sinusitis Mycobacterium avium complex disease (disseminated), treatment in persons with advanced HIV infection Mycobacterium avium complex disease(disseminated), prevention in persons with advanced HIV infection Otitis media, acute Pelvic inflammatory disease Pharyngitis/tonsillitis Pneumonia, community-acquired Respiratory tract infections ,lower Sexually transmitted diseases (urethritis, cervicitis, and chancroid) Skin and skin structure infections (uncomplicated) Susceptible infections due to *Chlamydia pneumoniae, C trachomatis, Haemophilus ducreyi, H influenza, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, M hominis, N gonorrhoeae, Staph aureus, Strep agalactiae, S pneumoniae, S pyogenes*	Chronic bronchitis, acute bacterial exacerbation Haemophilus infections Mycobacterial infections, disseminated Mycobacterium avium complex disease(disseminated), prevention in persons with advanced HIV infection Mycobacterium avium complex disease (disseminated), treatment in persons with advanced HIV infection Mycoplasma pneumoniae infections Otitis media, acute Pharyngitis/tonsillitis Pneumonia, community-acquired Respiratory tract infections ,lower Sinusitis, acute maxillary Skin and skin structure infections, uncomplicated H. pylori (when used in combination with omeprazole or ranitidine bismuth citrate or as triple therapy with amoxicillin and lansoprazole or omeprazole) Susceptible bacterial infections due to *Chlamydia pneumoniae, Haemophilus influenzae, H parainfluenzae, Helicobacter pylori, Moraxella catarrhalis, Mycobacterium avium, M intracellulare, Mycoplasma pneumoniae, Staph aureus, Strep pneumoniae, Strep pyogenes*

Place in Therapy

The increased use of macrolide antibiotics has been correlated with increased resistance rates to erythromycin in isolates of Group A Streptococci, and prescribing of macrolide antibiotics has increased in the United States. A high incidence of erythromycin-resistant group A streptococci (48%) was reported in a group of children attending the same school, and this high prevalence was also noted in the community. Routine use of macrolides for the treatment of pharyngitis caused by group A streptococci is not recommended as susceptibilities of group A streptococci to antibiotics such as penicillin remain stable. More epidemiologic and sensitivity data is needed to better characterize these resistance patterns.

Oral erythromycin is suggested by the American Heart Association as an alternative to clindamycin for prophylaxis of endocarditis for patients at risk undergoing dental, oral, or upper respiratory procedures, who are allergic to amoxicillin or penicillin.

Erythromycin is an appropriate alternative to penicillin and cephalosporin antimicrobials for infections with susceptible gram-positive and gram-negative bacteria. The drug is highly effective against Legionnaire's bacterium, *Mycoplasma pneumonia*, and *Chlamydia trachomatis*, and is the drug of first choice for these infections.

Erythromycin has been successfully utilized for acne vulgaris, otitis media, *Campylobacter enteritis*, neonatal conjunctivitis, Legionnaire's disease, preoperative bowel preparation, mycoplasma infections, chlamydia infections and most infections caused by gram-positive organisms.

Department of Veterans Affairs Formulary

- Azithromycin injection and oral
- Clarithromycin oral
- Erythromycin injections and oral

Summary of Pipeline / New Agents Expected to Offer Related Treatment Options

Telithromycin (Ketek®) is a semisynthetic derivative of erythromycin A belonging to the ketolides, a class of antibacterial agents related to macrolides. Approved in the United States April 1, 2004 – approved July 2001 in Europe. Telithromycin is an alternative for treatment of confirmed (laboratory) or suspected (poor clinical response to other antibiotics) multi-drug resistant infections secondary to gram-positive cocci, particularly pneumococcus. Telithromycin has not been approved for use in pediatric patients.

Class Effects:	Macrolides
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Erythromycin and the other macrolides attach to the 50S subunit of the bacterial ribosome. Although the exact stage of protein synthesis affected by the macrolides is unknown, they may interfere with the translocation reaction. The growing peptide chain with its t-RNA moves from the 'acceptor site' to the 'donor site' on the ribosome. The macrolides most likely bind to the donor site, preventing the translocation of the peptide chain.
Spectrum (innovator drug)	Erythromycin is most active against gram-positive bacteria, including most strains of penicillin-resistant *Staphylococci. Strep pyogenes, Strep pneumoniae*, and *Strep viridans* are highly sensitive and seldom require sensitivity tests in clinical practice. Although most staphylococci are still sensitive, resistant strains may be encountered, especially in hospitals. Sensitivity testing is always advisable in the hospital setting. *B anthracis, Listeria monocytogenes*, and *C diphtheria* are sensitive to erythromycin. Erythromycin also has a broad range of activity against gram-positive anaerobic organisms, including *Eubacterium, Propionibacterium, Bifidobacterium, Lactobacillus, Peptostreptococcus, Clostridium tetani, Cl perfringens, Actinomyces israelii*, and *Arachnia propionica*. While gram-negative enteric bacilli are generally very resistant to erythromycin, gram-negative coccobacilli show varying degrees of sensitivity. Most strains of Neisseria and H influenzae are susceptible. The drug is also active against *Neisseria, Bordetella, Brucella, Campylobacter*, and *Legionella. Treponema, Chlamydia*, and mycoplasma have also been susceptible to erythromycin. Antibacterial activity against gram-negative bacilli is influenced by pH with increased activity as the pH rises. Thus, most *E coli* and *Klebsiella* strains can be inhibited by erythromycin concentrations attained in urine with ordinary doses, provided the urine is alkalinized. Erythromycin is one of the most active drugs against the Legionnaires' disease bacterium. Anaerobic bacteria, including Bacteroides, can only be inhibited by high erythromycin concentrations attainable by parenteral administration. Erythromycin is inactive against *Enterobacteriaceae* and *Pseudomonas*. Erythromycin is highly effective against *Treponema pallidum, Chlamydia trachomatis*, and *Mycoplasma pneumoniae*. Erythromycin was successful as a single agent against *Mycobacterium chelonei*.
Pediatric Labeling	All have pediatric indications except for extended-release clarithromycin formulation (Biaxin® XL).
Contraindications	Hypersensitivity to any macrolide antibiotic Concomitant administration of clarithromycin or erythromycin with cisapride or pimozide Preexisting liver disease (erythromycin estolate)
Major AEs / Warnings	Gastrointestinal effects Individuals with prolonged QT interval Hepatic dysfunction

Class Effects:	Macrolides
Drug Interactions	As a class, the macrolides have been studied and reviewed extensively in regards to their drug interaction profiles. In general, the macrolides are classified into three groups based on their inhibition of cytochrome P450 3A4 in-vitro: ▪ Group 1 agents bind and strongly inhibit CYP 3A4. The group includes erythromycin. ▪ Group 2 agents have lower affinity for CYP 3A4 and form complexes to a lesser extents. The group includes clarithromycin. ▪ Group 3 agents bind poorly to CYP 3A4 and have little inhibitory activity. The group includes azithromycin. Drug interactions with macrolides may also occur via alterations in gastric emptying or by alteration of normal gastrointestinal microflora.[1] See Drug Interaction chart which follows for specific drugs.

Interacting Drugs	Erythromycin	Clarithromycin	Azithromycin
Theophylline	X	X	*
Digoxin	X	X	*
Oral anticoagulants	X	X	*
Ergotamine/ dihydroergotamine	X	X	*
Triazolam/ midazolam	X	X	*
Clozapine	X	X	
Carbamazepine	X	X	*
Cyclosporine	X	X	*
Felodipine	X	X	
Tacrolimus	X	X	
Methylprednisone	X	X	
Hexobarbital	X	X	*
Phenytoin	X	X	*
Alfentanil/sufentanil	X	X	
Cisapride	X	X	
Disopyramide	X	X	
HMG CoA reductase inhibitors	X	X	
Bromocriptine	X	X	
Valproate	X	X	
Terfenadine [discontinued]	X	X	*
Astemizole [discontinued]	X	X	
Pimozide	X	X	
Rifabutin	X	X	
Omeprazole		X	
Zidovudine		X	
Fluconazole		X	
Ritonavir		X	X

*Although azithromycin has not been found to interact with these agents, the package insert specifies that caution should be used due to interactions found with other macrolides.

Drug Class:	Macrolides		
Characteristic	**Erythromycin**	**Azithromycin** Zithromax®	**Clarithromycin** Biaxin®, Biaxin XL®
Structure-Activity		Azithromycin is the prototype of a subclass of macrolide antibiotics known as the azalides. This agent differs structurally from erythromycin by insertion of a methyl-substituted nitrogen at position 9a in the lactone ring, creating a 15-membered macrolide.	Chemically, clarithromycin differs from erythromycin only in that it possesses a methoxy group rather than a hydroxyl group at position 6 of the macrolide ring. This not only makes the compound more stable in the presence of gastric acid, but also changes its metabolic fate such that a very active 14-hydroxy-clarithromycin metabolite is formed; this metabolite is more active than the parent compound against *Haemophilus influenzae*.
Spectrum	See Class Review section	The antibacterial action of azithromycin is similar to erythromycin. Azithromycin has increased susceptibility against *Haemophilus influenzae, Haemophilus parainfluenza, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae, Campylobacter jejuni, Ureaplasma urealyticum*, and *Neisseria gonorrhoeae*.	More active than erythromycin against pathogens such as *Staphylococcus aureus, Streptococcus pyogenes*, and *Streptococcus pneumoniae*.
Pharmacology	An in-vitro study showed that erythromycin induces neutrophil apoptosis in a dose-dependent manner and directly proportional to duration of erythromycin exposure. In vivo, enhanced neutrophil apoptosis caused by erythromycin may inhibit tissue damage and inflammation by limiting the capacity of neutrophils to generate	Azithromycin has been found to have significant post-antibiotic effect in susceptible strains of microorganisms. The average length of post-antibiotic effect was 3.5 hours for S pyogenes and S pneumoniae, 3 hours for M catarrhalis and H influenzae, and 2 hours for Klebsiella species	The main metabolite of clarithromycin (i.e., 14-hydroxyl clarithromycin) is twice as active as clarithromycin against *Haemophilus influenzae*, but is 4 to 7 times less active than clarithromycin against MAC isolates. The clinical role of the 14-hydroxyl clarithromycin metabolite against susceptible bacteria has not been evaluated.

Drug Class:	Macrolides		
Characteristic	Erythromycin	Azithromycin Zithromax®	Clarithromycin Biaxin®, Biaxin XL®
	potentially injurious responses to inflammatory mediators. This mechanism may account for the efficacy of erythromycin in cases of diffuse panbronchiolitis and chronic sinusitis, even when the causative agent is Pseudomonas aeruginosa, a bacterium which is insensitive to erythromycin.		

Drug Class:	Macrolides		
Characteristic	**Erythromycin**	**Azithromycin** Zithromax®	**Clarithromycin** Biaxin®, Biaxin XL®
Date of FDA Approval		Nov 1991	Oct 1991
Generic available?	Yes	No	No Generic is tentatively approved for the immediate release and XL formulations. Ranbaxy expects to release their product after the patent expires for Biaxin on May 23, 2005.
Manufacturer (if single source)	Various	Pfizer	Abbott
Dosage forms / route of admin	**Erythromycin base** Tablets: 250 mg , 333 mg, 500 mg Capsules, delayed release: 250 mg **Erythromycin estolate** Suspension: 125 mg/5 ml, 250 mg/5 ml **Erythromycin stearate** Tablets: 250 mg, 500 mg **Erythromycin ethylsuccinate** Tablets: 400 mg Suspension: 200 mg/5 mg, 400 mg/5 ml **Erythromycin lactobionate** Injection: 500 mg, 1 gm	Tablet: 250 mg, 500 mg, 600 mg Powder for oral suspension: 100mg/5ml, 250mg/5ml, and single dose 1 gram packets. (Single dose packets should be reconstituted with 60 mL of water and the re-constituted mixture consumed immediately – the single dose packet is not indicated for pediatric use.) Injection: 500 mg	Granules for oral suspension: 125mg/5ml, 250mg/5ml Tablet, immediate-release: 250mg, 500mg (Biaxin® Filmtab), Tablet, extended-release: 500mg (Biaxin® XL Filmtab).
Dosing frequency	q 6h – q 12h	Once daily	BID (IR) Once daily (XL)
General dosing guidelines	The usual recommended dose is erythromycin 250 mg every 6 hours. If twice daily dosing is desired, the recommended dose is 500 mg every 12 hours. Higher doses may be used depending on	The usual adult dose is 500 mg on the first day as a single dose followed by 250 mg once daily on days 2 through 5. Acute bacterial exacerbations of COPD (mild to moderate) may alternatively receive 500 mg daily for 3 days.	Typical oral adult doses for immediate-release clarithromycin are 250 to 500 mg twice a day for 7 to 14 days. For the extended-release formulation, the recommended adult oral dose is 1000 mg (2 x 500 mg) once daily. In children, the recommended dose is 15

Drug Class:	Macrolides		
Characteristic	Erythromycin	Azithromycin Zithromax®	Clarithromycin Biaxin®, Biaxin XL®
	the severity of infection with the maximum daily dose at 4 grams. Twice daily dosing is not recommended if using doses larger than 1 g. Capsules containing enteric-coated pellets of erythromycin (ERYC®) may be opened and sprinkled on apple sauce for administration to patients that are unable to swallow the capsule whole.	Acute bacterial sinusitis – 500 mg daily x 3 days Non-gonoccocal urethritis and cervicitis or Chancroid – One single 1 gm dose Gonoccocal urethritis and cervicitis – One single 2 gm dose For the prevention of Mycobacterium avium complex (MAC) infection, the recommended dosage of azithromycin is 1200 mg once weekly. For the treatment of disseminated MAC infection, the recommended dose is 600 mg daily in combination with ethambutol 15 mg/kilogram (kg)/day. For pediatric patients, the dosage ranges from 5 mg/kg to 30 mg/kg once daily depending on the indication (acute bacterial sinusitis – 10 mg/kg x 3 days, acute otitis media, alternative regimen – 30 mg/kg as a single dose)	mg/kg/day in 2 divided doses. For Helicobacter infections, the recommended dosage for immediate-release clarithromycin is 500 mg 2 to 3 times daily in combination with other anti-H pylori drugs; low-dose regimens which used clarithromycin 250 mg have also been effective. Clarithromycin oral suspension and immediate release tablets can be taken with or without food. The extended release tablets should be taken with food.
FDA Labeled Indications	See table		
Other Studied Uses	Bite injuries Blepharokeratitis Bronchitis Campylobacter jejuni infections Chancroid Cholera Corynebacterium jeikeium infect Diphtheria	Acne Cholera Cystic fibrosis Endocarditis prophylaxis Gingival hyperplasia - drug-induced Legionella infections Lower respiratory tract infections, prophylaxis Lyme disease	Anthrax Asthma Endocarditis prophylaxis Lyme disease Cyclosporine dose reduction Mediterranean Spotted Fever Mycobacterial infections - other Pertussis

Drug Class:	Macrolides		
Characteristic	**Erythromycin**	**Azithromycin** Zithromax®	**Clarithromycin** Biaxin®, Biaxin XL®
	Eikenella corrodens infections Gastroparesis Genital mycoplasmas Impetigo Intraocular discitis Leptotrichia buccalis infections Lyme disease Moraxella catarrhalis infections Perinatal streptococcal disease prophylaxis Premature rupture of the membranes in pregnancy Preoperative bowel preparation Ureaplasm urealtyticum infection	Mediterranean Spotted Fever Mycoplasma pneumoniae infections Pertussis	Pharyngotonsillitis Pneumonia-legionella pneumophila Ureaplasma urealyticum infections
Pharmacokinetic Issues	Absorption is variable but much better with the various salt forms compared to the base; The drug is widely distributed in body tissues; Metabolism occurs in the liver by demethylation with excretion of 2.5% to 15% unchanged drug in the urine; Additional excretion and sequestration occurs in bile.	Peak serum levels of azithromycin are observed 3 to 4 hours following oral administration; Oral bioavailability is reportedly 38%; Tissue concentrations are significantly higher than serum levels; only small amounts of the drug are excreted in the urine, and the elimination half-life is biphasic.	Clarithromycin is well absorbed from the gastrointestinal tract, with peak plasma concentrations occurring about 2 to 4 hours after oral administration. Extensive tissue penetration is evident with the exception of the central nervous system. The serum half-life is approximately 3 to 7 hours. Clarithromycin is metabolized to its active 14-hydroxy metabolite, and also N-demethylated; metabolites are primarily eliminated renally.
Notes:	Erythromycin estolate suspension may be kept at room temperature for 14 days without significant loss of potency. The	Oral suspension and tablets may be taken with or without food.	Food will delay the absorption of immediate-release clarithromycin tablets and the formation of the metabolite, 14-

Drug Class:	Macrolides		
Characteristic	**Erythromycin**	**Azithromycin** Zithromax®	**Clarithromycin** Biaxin®, Biaxin XL®
	manufacturer recommends refrigeration to maintain optimal taste. Erythromycin ethylsuccinate (EES® 200 and 400) liquids require refrigeration to preserve taste until dispensed. Refrigeration by the patient is not required if used within 14 days.	Azithromycin and aluminum- and magnesium-containing antacids should not be administered simultaneously.	hydroxyclarithromycin; however, the extent of absorption is not affected by food. Do not refrigerate the suspension.
Key Populations			
Hepatic Impairment	Use with caution in patients with hepatic impairment		
Renal Impairment	Patients with severe renal failure (ClCr < 10 mL/min) should receive 50 to 75% of the normal dose at the usual dosing interval. No dosage adjustment is necessary for patients with mild to moderate renal failure (ClCr > 10 mL/min.	No dosage adjustment is needed in patients with renal insufficiency; however, use caution in patients with a ClCr <10 mL/min.	In the presence of severe renal impairment (i.e., ClCr <30 mL/min), the dose should be halved or the dosing interval doubled. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. However, for patients with renal impairment, the following dosage adjustments should be considered. For patients with CLCR 30 to 60 mL/min, the dose of clarithromycin should be reduced by 50%. For patients with CLCR < 30 mL/min, the dose of clarithromycin should be decreased by 75%.
Pregnancy	Pregnancy Category B Animal reproductive studies with erythromycin have demonstrated no evidence of teratogenicity.	Pregnancy Category B Animal studies using doses that exceed the recommended human dose of azithromycin have demonstrated no evidence of	Pregnancy Category C In animal studies, clarithromycin has had adverse effects on the outcome of pregnancy and/or the embryo-fetal development at doses producing serum levels 2 to 17 times

Drug Class:	Macrolides		
Characteristic	Erythromycin	Azithromycin Zithromax®	Clarithromycin Biaxin®, Biaxin XL®
	No well-controlled studies in pregnant women. In view of these facts, erythromycin should only be considered during pregnancy if the potential benefit of the drug outweighs the potential risk to the fetus. Erythromycin is excreted in human milk; caution should be used when drug is administered to a nursing woman.	carcinogenicity or teratogenicity. No well-controlled studies in pregnant women. Use caution before administering azithromycin to women of childbearing potential, especially during the first trimester when maximum organogenesis takes place.	therapeutic levels obtained in humans. Clarithromycin should not be used during pregnancy unless no alternative therapy is available.
Geriatric	Elderly patients receiving intravenous erythromycin at doses of 4 grams/day or more may be at an increased risk for developing drug-induced hearing loss, especially those with renal or hepatic impairment.	When studied in healthy elderly subjects aged 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.	Clarithromycin dosage adjustments are not required in healthy elderly patients. However, dosage adjustments should be considered in elderly patients with severe renal impairment.

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Abstracts

Int J Antimicrob Agents. 2001;18 Suppl 1:S11-5.

Advanced-generation macrolides: tissue-directed antibiotics.

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The azalide antibiotic azithromycin and the newer macrolides, such as clarithromycin, dirithromycin and roxithromycin, can be regarded as 'advanced-generation' macrolides compared with erythromycin, the first macrolide used clinically as an antibiotic. Their pharmacokinetics are characterized by a combination of low serum concentrations, high tissue concentrations and, in the case of azithromycin, an extended tissue elimination half-life. Azithromycin is particularly noted for high and prolonged concentrations at the site of infection. This allows once-daily dosing for 3 days in the treatment of respiratory tract infections, in contrast to longer dosage periods required for erythromycin, clarithromycin, roxithromycin and agents belonging to other classes of antibiotics.

The spectrum of activity of the advanced-generation macrolides comprises Gram-positive, atypical and upper respiratory anaerobic pathogens. Azithromycin and the active metabolite of clarithromycin also demonstrate activity against community-acquired Gram-negative organisms, such as Haemophilus influenzae. Advanced-generation macrolides, and in particular azithromycin, are highly concentrated within polymorphonuclear leucocytes, which gravitate by chemotactic mechanisms to sites of infection. Following phagocytosis of the pathogens at the infection site, they are exposed to very high, and sometimes cidal, intracellular concentrations of antibacterial agent. Pharmacodynamic models and susceptibility breakpoints derived from studies with other classes of drugs, such as the beta-lactams and aminoglycosides, do not adequately explain the clinical utility of antibacterial agents that achieve high intracellular concentrations. In the case of azithromycin, attention should focus on tissue pharmacokinetic and pharmacodynamic concepts.

Drugs. 2001;61(4):443-98.

Review of macrolides and ketolides: focus on respiratory tract infections.

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The first macrolide, erythromycin A, demonstrated broad-spectrum antimicrobial activity and was used primarily for respiratory and skin and soft tissue infections. Newer 14-, 15- and 16-membered ring macrolides such as clarithromycin and the azalide, azithromycin, have been developed to address the limitations of erythromycin. The main structural component of the macrolides is a large lactone ring that varies in size from 12 to 16 atoms. A new group of 14-membered macrolides known as the ketolides have recently been developed which have a 3-keto in place of the L-cladinose moiety. Macrolides reversibly bind to the 23S rRNA and thus, inhibit protein synthesis by blocking elongation. The ketolides have also been reported to bind to 23S rRNA and their mechanism of action is similar to that of macrolides.

Macrolide resistance mechanisms include target site alteration, alteration in antibiotic transport and modification of the antibiotic. The macrolides and ketolides exhibit good activity against gram-positive aerobes and some gram-negative aerobes. Ketolides have excellent activity versus macrolide-resistant Streptococcus spp. Including mefA and ermB producing Streptococcus pneumoniae. The newer macrolides, such as azithromycin and clarithromycin, and the ketolides exhibit greater activity against Haemophilus influenzae than erythromycin.

The bioavailability of macrolides ranges from 25 to 85%, with corresponding serum concentrations ranging from 0.4 to 12 mg/L and area under the concentration-time curves from 3 to 115 mg/L x h. Half-lives range from short for erythromycin to medium for clarithromycin, roxithromycin and ketolides, to very long for dirithromycin and azithromycin. All of these agents display large volumes of distribution with excellent uptake into respiratory tissues and fluids relative to serum. The majority of the agents are hepatically metabolised and excretion in the urine is limited, with the exception of clarithromycin.

Clinical trials involving the macrolides are available for various respiratory infections. In general, macrolides are the preferred treatment for community-acquired pneumonia and alternative treatment for other respiratory infections. These agents are frequently used in patients with penicillin allergies. The macrolides are well-tolerated agents. Macrolides are divided into 3 groups for likely occurrence of drug-drug interactions: group 1 (e.g. erythromycin) are frequently involved, group 2 (e.g. clarithromycin, roxithromycin) are less commonly involved, whereas drug interactions have not been described for group 3 (e.g. azithromycin, dirithromycin). Few pharmacoeconomic studies involving macrolides are presently available. The ketolides are being developed in an attempt to address the increasingly prevalent problems of macrolide-resistant and multiresistant organisms.

J Am Dent Assoc. 1999 Sep;130(9):1341-3.

Dental therapeutic indications for the newer long-acting macrolide antibiotics.

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BACKGROUND: When treating oral infections, clinicians have used the macrolide antibiotic erythromycin as an alternative antibiotic for patients who have documented allergic reactions to penicillins. In this article, the author reports on his assessment of the pharmacology of erythromycin and the newer macrolide antibiotics, as well as of their indications for the prevention of bacterial endocarditis and their possible use for oral-dental infections.

TYPES OF STUDIES REVIEWED: The author reviewed the current clinical pharmacology literature with specific emphasis on reports indicating these antibiotics' efficacy in treating oral-dental infections.

RESULTS: Azithromycin, clarithromycin and dirithromycin are erythromycin analogues that are currently marketed in the United States. All three have the therapeutic advantages over erythromycin of longer durations of action, enhanced acid stabilities and improved tissue distributions. A lower incidence of gastrointestinal distress and abdominal cramping is reported for all three of these newer agents than for erythromycin. Azithromycin and dirithromycin do not appear to compete for the same hepatic drug-metabolizing enzymes as erythromycin and therefore are not associated with the same drug interactions.

CONCLUSIONS AND CLINICAL IMPLICATIONS: The newer macrolide antibiotics offer the advantage of fewer adverse gastrointestinal effects than erythromycin and dosing regimens of only once or twice a day. Yet, the extremely high price of the newer macrolides compared with that of erythromycin limits their routine use.

J Antimicrob Chemother. 1998 Feb;41(2):289-91.

Activity of azithromycin, clarithromycin, roxithromycin, dirithromycin, quinupristin/dalfopristin and erythromycin against Legionella species by intracellular susceptibility testing in HL-60 cells.

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We evaluated a human monocyte cell line (HL-60) as a model for testing the intracellular activity of anti-Legionella antibiotics; 1.5 x 10(6) HL-60 cells/well were differentiated into adherent cells and infected with 1.5 x 10(7) cfu of Legionella pneumophila. The most active agents against L. pneumophila as judged by broth dilution MICs were (in order of activity) azithromycin, clarithromycin, roxithromycin, quinupristin/dalfopristin, erythromycin and dirithromycin. The most active inhibitors of L. pneumophila intracellular multiplication were (in order of activity) azithromycin, erythromycin, quinupristin/dalfopristin, roxithromycin, dirithromycin and clarithromycin. All the agents were highly active against Legionella micdadei and Legionella bozemanii when compared with L. pneumophila.

J Chemother. 2002 Aug;14(4):384-9.

Comparative analysis of azithromycin and clarithromycin efficacy and tolerability in the treatment of chronic prostatitis caused by Chlamydia trachomatis.

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A total of 123 patients, older than 18 years of age, with symptoms of chronic prostatitis and inflammatory findings as well as the presence of Chlamydia trachomatis confirmed by DNA/RNA DIGENE hybridization method in expressed prostatic secretion or in voided bladder urine collected immediately after prostatic massage, were examined. The patients were randomized to receive a total of 4.5 g of azithromycin for 3 weeks, given as a 3-day therapy of 1 x 500 mg weekly or clarithromycin 500 mg b.i.d. for 15 days. Patients' sexual partners were treated at the same time. Clinical and bacteriological efficacy were evaluated 4-6 weeks after the end of therapy.

In the group of patients with chronic chlamydial prostatitis the eradication rates (azithromycin 37/46, clarithromycin 36/45) and the clinical cure rates (azithromycin 32/46, clarithromycin 32/45) were not significantly different with regards to the administered drug ($p > 0.05$). In the group of patients with asymptomatic chlamydial prostatitis the eradication rates (azithromycin 11/16, clarithromycin 10/15) were not significantly different with regards to the administered drug ($p = 1.00$, OR = 1.1).

Eur J Clin Microbiol Infect Dis. 2002 Jun;21(6):427-31. Epub 2002 Jun 11.

Double-blind, placebo-controlled study comparing the effect of azithromycin with clarithromycin on oropharyngeal and bowel microflora in volunteers. *

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The purpose of this double-blind study was to assess the effect of azithromycin and clarithromycin on oral and fecal microflora. Bacterial species from fecal samples and throat washes from healthy volunteers were identified and quantified before, during and after receipt of either placebo (n=6), azithromycin (500 mg once daily for 3 days; n=6) or clarithromycin (500 mg twice daily for 7 days; n=6). In both antibiotic groups, the changes in oropharyngeal aerobic microflora following antibiotic administration were minor. Antibiotics neither changed the bacterial load of Streptococcus spp. compared with placebo, nor did macrolide-resistant streptococci emerge.

In the fecal aerobic microflora, the number of organisms of the family Enterobacteriaceae decreased slightly after antibiotic administration in both the clarithromycin and the azithromycin groups, but levels normalized by day 21 after therapy. No colonization with nonfermenters or Clostridium difficile was seen, and the total number of anaerobic bacteria was not affected in any study group.

In conclusion, there were no significant differences between azithromycin and clarithromycin in their effect on human oropharyngeal and intestinal microflora, nor was the use of these antibiotics associated with colonization by resistant, gram-positive organisms or overgrowth of opportunistic microorganisms.

* This study was made possible by a grant from Pfizer, The Netherlands

Drug Class:	Cephalosporins: Third-Generation			
Drugs Reviewed:	Cefdinir	Cefpodoxime	Ceftibuten	Cefditoren
	Omnicef®	Vantin®	Cedax®	Spectracef®

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

There are currently four third-generation cephalosporins available in the United States as indicated above.

- One unique aspect of this class is its superior activity against gram-negative bacilli resistant to other beta-lactam antibiotics. Since these relatively resistant bacilli are rarely the cause of community acquired infection, use of this class for these infections is discouraged.
- Oral third generation agents are active against the pathogens responsible for acute otitis media, but GI side effects and higher cost limit their usefulness.
- These agents are active against most clinically important *Enterobacteriaceae* and have been used to treat uncomplicated urinary tract infections; however, they offer no advantage over equally effective, less expensive agents.
- In summary, although the agents within this class can be considered therapeutic alternatives, their overall use should be very selective.

Spectrum

In general, and with some notable exceptions, 3rd generation cephalosporins have potent activity against *S. pneumoniae* (including some strains with elevated penicillin MIC), *S. aureus, H. influenzae, M. catarrhalis, Neisseria* spp., *E. coli, Klebsiella pneumoniae,* and *P. mirabilis.*

3rd generation cephalosporins are not effective against methicillin-resistant *S. aureus* or highly resistant penicillin-resistant *S. pneumoniae* .

This category is the most resistant to β-lactamase produced by gram-negative organisms.

Oral third generation agents do attain higher concentrations in the cerebrospinal fluid than other cephalosporins.

These agents are active against most clinically important *Enterobacteriaceae* and have been used to treat uncomplicated urinary tract infections; however, they offer no advantage over equally effective, less expensive agents.

Cefdinir: Cefdinir oral suspension is preferred over several other antibiotic suspensions, due to improved palatability. Overall taste ranking of antibiotics, from highest to lowest, was loracarbef > cefdinir > cefixime > azithromycin > ciprofloxacin > TMP-SMX > clarithromycin > trimethoprim > amoxicillin/clavulanate > cefpodoxime > cefuroxime.

The potential advantage of cefdinir over other oral cephalosporins is its good in-vitro activity against gram-positive organisms. However, although superior in-vitro to cefaclor and cephalexin, it has not always been more active than cefixime or cefpodoxime against gram-positive pathogens. There is no significant activity advantage of cefdinir over cefpodoxime or cefixime for gram-negative organisms.

Cefpodoxime:. Cefpodoxime is an extended-spectrum cephalosporin. It is most often classified as 3rd generation, but also exhibits 2nd-generation characteristics. Cefpodoxime has activity against *S. aureus.*

Cefditoren: Cefditoren is only indicated for adults and adolescents and is only available in tablet form. Cefditoren decreases serum concentration of carnitine, the clinical significance of this in normal patients is unclear. Tablets are formulated with a milk protein and should not be given to patients with milk protein hypersensitivity.

Available clinical data support the efficacy of oral cefditoren pivoxil in a variety of infections, including pneumonia and acute exacerbations of chronic bronchitis; it has fairly good activity against penicillin-resistant pneumococcus. However,

the drug has not proven more efficacious than second-generation oral cephalosporins; a significant advantage over penicillin V was not evident several weeks after treatment in streptococcal pharyngitis patients. There are no comparisons with other oral third-generation cephalosporins (e.g., ceftibuten, cefdinir, cefpodoxime proxetil).

Ceftibuten: Ceftibuten is a broad-spectrum, orally active third-generation cephalosporin. It has a spectrum of activity comparable to cefprozil, cefuroxime axetil, cefetamet pivoxil, cefpodoxime proxetil, and cefixime. It does not have activity against *S. aureus.*

The clinical applications of ceftibuten will most likely include respiratory tract infections caused by Haemophilus spp, penicillin sensitive pneumococci, beta-hemolytic streptococci, Moraxella catarrhalis, and streptococcus pyogenes. Although it has been claimed that ceftibuten produces higher serum levels than other cephalosporins, comparative trials are lacking and the clinical importance of this claim has not been proven.

- Cefixime and cefpodoxime are slowly absorbed and reach lower maximal serum concentrations relative to the other orally administered 3rd generation cephalosporins.
- Contraindications, warnings, adverse drug events, and drug interactions are similar for all third-generation cephalosporins and are considered class effects. Refer to *Class Effects* table for more details.

Summary of Indications (Oral Formulations)

FDA labeled Indications	Cefdinir	Cefpodoxime	Ceftibuten	Cefditoren
	Omnicef®	Vantin®	Cedax®	Spectracef®
bronchitis	✓	✓	✓	✓
gonorrhea		✓		
otitis media	✓	✓	✓	
pharyngitis/tonsillitis	✓	✓	✓	✓
pneumonia	✓	✓		✓
sinusitis	✓	✓		
skin and soft tissue infections	✓	✓		✓
urinary tract infections		✓		
✓ = FDA approved indication				

Place in Therapy

Sinusitis

The recommendation for the management of mild sinusitis is symptomatic treatment and reassurance. Antibiotic therapy should be reserved for patients with moderately severe symptoms who meet the criteria for the clinical diagnosis of acute bacterial sinusitis (symptoms that last >7 days and include maxillary pain in the face or teeth and purulent nasal secretions) and for those with severe rhinosinusitis symptoms, regardless of duration of illness.

In patients with acute bacterial sinusitis, the use of first-line agents (amoxicillin, trimethoprim-sulfamethoxazole) is associated with similar clinical benefits and significant cost savings when compared to second-line agents (fluoroquinolones, azithromycin, clarithromycin, second- and third-generation cephalosporins). Appropriate choice of narrow-spectrum antibiotics will also decrease the risk for emergence and spread of antibiotic-resistant bacteria. [6-8]

Acute Otitis Media

From the CDC working group: Acute Otitis Media: Management and surveillance in an era of pneumococcal resistance: a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working group.

The CDC working group concluded that amoxicillin should remain the first line antimicrobial for treating acute otitis media (with an increase in empiric treatment from 40-45 mg/kg/day to 80-90 mg/kg/day). The CDC Working group chose three treatment regimens for children who have failed amoxicillin on Day 3 or Days 10-28: high dose amoxicillin/clavulanate; cefuroxime axetil or intramuscular ceftriaxone. Children allergic to or intolerant to amoxicillin or other beta-lactam antibiotics use clarithromycin or azithromycin.

Department of Veterans Affairs Formulary

Cefpodoxime proxetil oral

Summary of Pipeline Agents Expected to Offer Related Treatment Options

BAL-5788 (Basilea Pharmaceutica) - fourth-generation cephalosporin antibiotic with activity against Gram-negative and multi-resistant Gram-positive organisms, including methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-resistant Streptococcus pneumoniae (PRSP), for treatment of bacterial infections, intravenous formulation. Phase II complete; Phase III planned for the second half of 2004 (as of 5/2004).

PPI-0903 (Takeda Chemical Industries) - broad-spectrum cephalosporin antibiotic/water soluble prodrug of Takeda's T-91825 with activity against Gram-positive and Gram-negative pathogens, including Methicillin-Resistant Staphylococcus aureus (MRSA), Vancomycin Intermediate Staphylococcus aureus, Linezolid-resistant S. aureus, and penicillin-resistant Streptococcus pneumoniae (PRSP), for treatment of serious bacterial infections in hospitalized patients, intravenous formulation. Phase I initiated 5/2004

Class Effects:	Cephalosporins: Third-Generation
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Third-generation oral cephalosporins, like other beta-lactam antibiotics, inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs). They inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. It is thought that the beta-lactam antibiotics inactivate transpeptidase via acylation of the enzyme with cleavage of the CO-N bond of the beta-lactam ring. Upon exposure to beta-lactam antibiotics, bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Contraindications	▪ Known allergy to the cephalosporin group of antibiotics ▪ Carnitine deficiency for cefditoren
Major AEs / Warnings	▪ Hypersensitivity reactions are possible and may require epinephrine and other emergency measures ▪ Use with caution in patients with a history of hypersensitivity to penicillins ▪ Pseudomembranous colitis should be considered in patients developing diarrhea while being treated
Drug Interactions	▪ May potentiate the nephrotoxicity of aminoglycosides. ▪ Tetracycline derivatives may impair bactericidal effects of cephalosporins. ▪ Probenecid inhibits renal excretion.
Key Populations	
Renal Impairment	Since the cephalosporins are renally excreted, dosage adjustment (usually increased dosage intervals) is usually recommended (see table below for specific recommendations).
Pregnancy	Pregnancy Category B
Geriatric	Dosage adjustment is not necessary in elderly subjects with normal serum creatinine values.
Race	Although there is no data to support differences in efficacy of the third-generation cephalosporins in different races, it has been noted that the incidence of invasive *S. pneumoniae* infection is greater (2.6 times higher) in the African American population than the Caucasian population.

Drug Class:	Cephalosporins: Third-Generation			
Characteristic	**Cefdinir**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Vantin®	Cedax®	Spectracef®
Date of FDA Approval	Dec 1997	Aug 1992	Dec 1995	Aug 2001
Generic available?	No	Yes	No	No
Manufacturer (if single source)	Abbott		Biovail	Purdue Pharma
Dosage forms / route of admin	Capsules: 300 mg Suspension: 125 mg/5mL, 250 mg/5 ml	Tablet: 100 mg, 200 mg Suspension: 50 mg/5 ml, 100 mg/5 ml	Capsule: 400 mg Suspension: 90 mg/5mL, 180 mg/5 ml	Tablet: 200 mg
Dosing frequency	Once daily - BID	BID	Once daily - BID	BID
General dosing guidelines	The usual oral dose of cefdinir in adults and adolescents is 300 mg orally twice daily. An oral dose of 600 mg once daily has been used in bronchitis, sinusitis and pharyngitis/tonsillitis. In children, doses of either 7 mg/kg orally twice daily or 14 mg/kg orally once daily have been administered for otitis, pharyngitis/tonsillitis, and sinusitis.	The recommended adult dosage is 100 to 400 mg twice daily for up to 14 days depending on the severity of infection. The usual pediatric dosage is 5 mg/kg twice daily for up to 10 days depending on the infection. Uncomplicated gonorrhea – 200 mg as a single dose	In adults, the usual dose is 400 mg daily for 10 days. In children a dose of 9 mg/kg/day for 10 days has been administered.	For the treatment of CAP and acute exacerbation of chronic bronchitis, the usual dose is 400 mg BID for 14 and 10 days, respectively. The dose for the treatment of pharyngitis/ tonsillitis and uncomplicated skin and skin structure infections is 200 mg BID for 10 days. Should be taken with meals.
Pediatric Labeling	= 6 months of age	= 2 months of age	= 6 months of age	= 12 years of age
Other Studied Uses	Vaginitis	Cystic fibrosis	Enteric infections Gynecologic infections Pneumonia Gonococcal urethritis Complicated UTI	Otitis media UTI

Drug Class:	Cephalosporins: Third-Generation			
Characteristic	**Cefdinir**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Vantin®	Cedax®	Spectracef®
Drug Interactions (other than class effects)	Iron supplements, antacids reduce absorption.	Antacids and H2 antagonists reduce Cmax and AUC.	H2 antagonists – ranitidine increased Cmax and AUC – clinical significance of these increases is not known	Should not be taken concomitantly with antacids or other drugs taken to reduce stomach acid.
Major AEs / Warnings (other than class effects)	Diarrhea is a frequent adverse effect of cefdinir (up to 15% of patients). Eosinophilia and abnormal liver function tests have been reported with higher than usual doses.	Eosinophilia has occurred during cefpodoxime therapy; headaches and asthenia have been reported in isolated instances. Diarrhea, abdominal pain, and nausea and vomiting have also occurred. Candidal vaginitis has been reported with cefpodoxime therapy. Urticaria, skin eruptions, and dermal mycoses have occurred.	Gastrointestinal disturbances may occur, including nausea, vomiting, diarrhea, and heartburn. Rare elevations in liver function tests have also occurred.	Nausea, diarrhea, abdominal pain, headache, eosinophilia, vaginal moniliasis, elevation of liver enzymes, and rash have been reported. Tablets contain sodium caseinate, a milk protein. Should not be administered to patients with milk protein sensitivity (not lactose intolerance). Not recommended for prolonged use (other pivalate-containing compounds have caused clinical manifestations of carnitine deficiency.

Drug Class:	Cephalosporins: Third-Generation			
Characteristic	**Cefdinir**	**Cefpodoxime**	**Ceftibuten**	**Cefditoren**
	Omnicef®	Vantin®	Cedax®	Spectracef®
Pharmacokinetic issues	Cefdinir is slowly absorbed after oral doses, with peak serum levels occurring within 4 hours. Cefdinir is excreted in the urine and has an elimination half-life of 1 to 4 hours. Should be taken 2 hours before or 2 hours after antacids.	Oral cefpodoxime is a prodrug, administered as the proxetil ester, which is absorbed and rapidly hydrolyzed to active cefpodoxime in the gut. Peak plasma concentrations are reached 2 to 3 hours after oral administration. Half-life is approximately 2.5 hours in patients with normal renal function. Take tablets with food. Take suspension with or without food.	Ceftibuten is rapidly absorbed, producing peak serum levels 2 to 3 hours after oral administration. Ceftibuten is excreted primarily unchanged in the urine with an elimination half-life of approximately 2 hours. Suspension should be taken 2 hours before a meal or at least 1 hour after a meal.	Cefditoren pivoxil is a prodrug, and is hydrolyzed in the intestinal wall to cefditoren. Peak cefditoren plasma levels occur in 1.5 to 3 hours. Cefditoren is mainly eliminated by the kidneys. The elimination half-life of cefditoren is 1 to 2 hours.
Renal Impairment	A dose of cefdinir 300 mg once daily is recommended for adult patients with ClCr <30 mL/min. Patients on hemodialysis – 300 mg after dialysis, followed by 300 mg every other day	In patients with severe renal impairment (ClCr <30 mL/min) the dosing interval for cefpodoxime should be increased to every 24 hours. Patients on hemodialysis – dosing frequency should be 3 times/week after dialysis	For patients with a ClCr of 30 to 49 mL/min a dose of 200 mg daily is recommended. For patients with a ClCr 5 to 29 mL/min, a dose of 100 mg daily is recommended. Patients on hemodialysis – 400 mg after each dialysis session	For patients with a ClCr between 30 to 49 mL/min/1.73 m^2, the maximum dose of cefditoren should be 200 mg BID. For patients with a Clcr less than 30 mL/min, the dose should be reduced to 200 mg every day.

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12. Product Information. Cedax (ceftibuten) capsules and suspension. Biovail Morrisville, NC (revised 3/2002) reviewed 10/2004.
13. Product Information. Spectracef (cefditoren) tablets. Purdue Pharmaceuticals Stamford, CT (revised 8/2003) reviewed 10/2004.
14. Product Information. Omnicef (cefdinir) capsules and suspension. Abbott Laboratories, Chicago, IL (revised 1/2004) reviewed 10/2004.

Abstracts

Infection. 1990;18 Suppl 3:S155-67.

Antibacterial activity and beta-lactamase stability of eleven oral cephalosporins

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Oral cephalosporins (cefixime, cefdinir, cefetamet, ceftibuten, cefpodoxime, loracarbef, cefprozil, cefuroxime, cefaclor, cefadroxil and BAY 3522) were compared by their antibacterial profile including stability against new beta-lactamases. Both activity and antibacterial spectrum of compounds structurally related to third generation parenteral cephalosporins (of the oximino class) were superior to established compounds. Activity against staphylococci was found to be highest for cefdinir, cefprozil and BAY 3522.

Cefetamet, ceftibuten and cefixime demonstrate no clinically meaningful antistaphylococcal activity while the other compounds investigated demonstrate intermediate activity. The antibacterial spectrum was broadest for cefdinir and cefpodoxime. New oral cephalosporins are equally inactive as established compounds against Enterobacter spp., Morganella, Listeria, Pseudomonas and Acinetobacter spp., methicillin-resistant staphylococci, Enterococcus spp., penicillin-resistant pneumococci and anaerobes.

New extended broad-spectrum betalactamases (TEM-3, TEM-5, TEM-6, TEM-7, SHV-2, SHV-3, SHV-4, SHV-5, CMY-1, CMY-2, and CTX-M) are active against the majority of oral cephalosporins. Ceftibuten, cefetamet, cefixime and cefdinir were stable against some of these enzymes even to a higher extent than parenteral cephalosporins. New oral cephalosporins should improve the therapeutic perspectives of oral cephalosporins due to their higher activity against pathogens marginally susceptible to established compounds (higher multiplicity of maximum plasma concentrations over MICs of the pathogens) and furthermore by including in their spectrum organisms resistant to established absorbable cephalosporins (e.g. Proteus spp., Providencia spp., Citrobacter spp., and Serratia spp.).

Infection. 1991 Sep-Oct;19(5):353-62.

Antibacterial activity of cefpodoxime in comparison with cefixime, cefdinir, cefetamet, ceftibuten, loracarbef, cefprozil, BAY 3522, cefuroxime, cefaclor and cefadroxil.

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The new oral cephalosporins cefpodoxime, cefixime, cefdinir, cefetamet and ceftibuten demonstrate enhanced activity against Enterobacteriaceae susceptible to the established compounds as well (e.g. cefuroxime, cefaclor, cefadroxil). In addition, cefpodoxime, cefixime, cefdinir, cefetamet and ceftibuten include in their spectrum species hitherto resistant to oral cephalosporins (Proteus vulgaris, Providencia spp., Yersinia enterocolitica). Besides, the majority of these compounds demonstrate relevant activity (MIC50 equal to or below 2 mg/l) against Enterobacter spp., Citrobacter freundii, Serratia spp. and Morganella morganii.

Ceftibuten is the most potent oral cephalosporin against most of the Enterobacteriaceae. Non-fermentative bacilli (Acinetobacter spp., Pseudomonas spp.) remain completely resistant to oral cephalosporins (except some Acinetobacter species against cefdinir and Pseudomonas cepacia against ceftibuten). Antistaphylococcal activity for oral cephalosporins is highest for cefdinir followed by BAY 3522, cefprozil, cefuroxime and cefpodoxime. Loracarbef, cefaclor and cefadroxil are about equally active, while the other compounds are only weakly active (cefixime) or inactive (cefetamet, ceftibuten). Enterococci are insensitive to new generation oral cephalosporins as they have been to established compounds.

The most active oral cephalosporins against hemolytic streptococci are cefdinir and cefprozil. Streptococcus pneumoniae, Streptococcus milleri and Streptococcus mitior are most susceptible to cefpodoxime, cefdinir, cefuroxime and BAY 3522. Penicillin resistant pneumococci have to be regarded as resistant to all oral cephalosporins. Fastidious pathogens like Haemophilus spp., Moraxella catarrhalis and Neisseria gonorrhoeae are more susceptible to cefpodoxime, cefixime, cefdinir, cefetamet and ceftibuten than to the other oral cephalosporins. The activity of oral cephalosporins is only weak against Listeria spp., Helicobacter pylori and anaerobic pathogens (except BAY 3522). Bordetella pertussis remains resistant to all absorbable cephalosporins.

Progress in antibacterial activity of oral cephalosporins was mainly achieved by cefpodoxime, cefixime, cefdinir, cefetamet and ceftibuten against Enterobacteriaceae and the fastidious pathogens and against staphylococci and the nonenterococcal streptococci by cefdinir, BAY 3522, cefprozil and cefpodoxime.

Int J Antimicrob Agents. 2003 Apr;21(4):313-8.

In-vitro activity of eight oral cephalosporins against Borrelia burgdorferi.

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Oral cephalosporins have not previously been extensively tested against larger numbers of Borrelia burgdorferi isolates derived from different clinical and geographical sources. This study investigated the in-vitro activity of eight oral cephalosporins in addition to ceftriaxone and apramycin, against 17 isolates of the B. burgdorferi complex, including one B. valaisiana and one B. bissettii tick isolate. Minimal inhibitory concentrations and minimal borreliacidal concentrations providing 100% killing of the final inoculum were determined by a standardized methodology in Barbour-Stoenner-Kelly-medium after 72 h of incubation.

The rank order of potency was ceftriaxone>cefuroxime-axetil>cefixime, cefdinir>cefpodoxime>cefaclor >ceftibuten, loracarbef>cefetamet-pivoxil, apramycin. Our study demonstrates the superior in-vitro effectiveness of ceftriaxone with good to excellent activity with the oral agents cefuroxime-axetil, cefixime and cefdinir against B. burgdorferi under strictly standardized test conditions.

Clin Ther. 2003 Jan;25(1):169-77.

Activity of nine oral agents against gram-positive and gram-negative bacteria encountered in community-acquired infections: use of pharmacokinetic/pharmacodynamic breakpoints in the comparative assessment of beta-lactam and macrolide antimicrobial agents. *

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BACKGROUND: The application of pharmacokinetic (PK) and pharmacodynamic (PD) data in conjunction with minimum inhibitory concentrations (MICs) of antibacterial agents has been shown to allow for improved selection and appropriate dosing of antimicrobial agents for specific infections, increasing the likelihood of bacteriologic cure and, through this, reducing the risk for the development of resistant organisms.

OBJECTIVES: This study was undertaken to provide data on current levels of resistance among common community-acquired bacterial species to 7 betalactam antimicrobial agents (including the combination product amoxicillin/clavulanate), azithromycin, and clarithromycin, determined through application of the PK/PD breakpoints based on time-above-MIC for the beta-lactams and the nonazalide macrolide clarithromycin, and on 24-hour serum area under the curve divided by MIC for the azalide macrolide azithromycin.

METHODS: The antimicrobial products tested were amoxicillin/clavylanate, cefpodoxime, cefdinir, cefditoren, cefprozil, cefuroxime, cefixime, azithromycin, and clarithromycin. The bacterial species comprised 70 penicillin-susceptible, 68 penicillin-intermediate, and 69 penicillin-resistant strains of Streptococcus pneumoniae; 46 beta-lactamase-positive and 54 beta-lactamase-negative strains of Haemophilus influenzae; 49 strains of Moraxella catarrhalis; and 100 methicillin-sensitive strains of Staphylococcus aureus (MSSA). Strains were isolated from clinical specimens obtained from outpatient-acquired infections in 1 clinical center in the Northeast and 1 in the north-central area of the United States within the past 2 years. National Committee for Clinical Laboratory Standards microdilution MIC methodology was used. PK/PD breakpoints were obtained from previously published studies and were based on blood values.

RESULTS: Amoxicillin/clavulanate was the product to which the greatest percentage of susceptible, intermediate, and resistant strains of pneumococci were sensitive at the PK/PD breakpoint, followed by cefditoren, cefpodoxime, cefuroxime, cefdinir, and cefprozil. None of the cephalosporins were active against penicillin-resistant pneumococci. Cefditoren and cefpodozime were the agents to which the greatest percentage of beta-lactamase-positive and beta-lactamase-negative strains of H influenzae were sensitive, followed by amoxicillin/clavulanate, cefdinir, and cefuroxime. Cefprozil was inactive against H influenzae. All of the beta-lactam products were active against M catarrhalis. All but cefpodoxime, cefditoren, and cefixime were active against MSSA.

CONCLUSIONS: In this study, based on PK/PD breakpoints, amoxicillin/clavulanate had the best overall activity of the 9 antimicrobial products tested. Cefpodoxime and cefditoren were active against >or=90% of strains of penicillin-susceptible and penicillin-intermediate pneumococci, H influenzae, and M catarrhalis. The macrolides azithromycin and clarithromycin were

active against penicillin-susceptible and penicillin-intermediate pneumococci and M catarrhalis; they were inactive against H influenzae and penicillin-resistant pneumococci.

* This study was supported by Pharmcia and Upjohn (Peapack, N.J.)

J Antimicrob Chemother. 1997 Feb;39(2):141-8.

Time-kill studies on susceptibility of nine penicillin-susceptible and -resistant pneumococci to cefditoren compared with nine other beta-lactams. *

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Broth MIC and time-kill methodology was used to determine the activity of cefditoren relative to those of penicillin G, ampicillin, amoxicillin, WY-49605, cefuroxime, cefpodoxime, cefdinir, cefixime and cefaclor against three penicillin-susceptible, three intermediate and three penicillin-resistant pneumococci. MICs of all agents rose with those of penicillin G. Cefditoren was the most active agent (MICs 0.002-0.5 mg/L), followed by WY-49605 (0.008-1.0 mg/L), amoxicillin (0.015-2.0 mg/L), cefuroxime (0.015-4.0 mg/L), cefpodoxime (0.03-4.0 mg/L), ampicillin (0.015-8.0 mg/L), cefdinir (0.03-16.0 mg/L), cefixime (0.125-64.0 mg/L) and cefaclor (0.5-128.0 mg/L).

All beta-lactams were bactericidal at the MIC after 24 h, and produced 90% killing after 12 h at concentrations above the MIC. Bactericidal concentrations of cefditoren, even for penicillin-resistant strains, were < or = 0.5 mg/L at 24 h. Additionally, cefditoren and WY-49605 were the only compounds that killed 99% of all strains after 6 h at > or = 4 x MIC. Cefditoren and amoxicillin killed 90% of all strains at 8 x MIC, and WY-49605 at 4 x MIC, after 4 h. Ampicillin had time-kill kinetics similar to those of amoxicillin, but MICs were 1-2 dilutions higher than the latter drug. Cefuroxime and cefpodoxime were the most active of other oral cephalosporins tested. Cefditoren and WY-49605 had the lowest MICs and most favourable time-kill kinetics of all beta-lactams tested.

* This study was supported by a grant from Meiji Seika Pharma International, Ltd, Tokyo, Japan

Drug Class:	Pegylated Interferon Alpha Products	
Drugs Reviewed:	Peginterferon alfa-2a (Pegasys®)	Peginterferon alfa-2b (PEG-Intron®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently two pegylated interferon alpha products available in the United States as indicated above
- Nonpegylated interferon alfa-2b plus ribavirin was previously a recommended first-line therapy in patients with chronic hepatitis C. Peginterferon alfa-2b or peginterferon alfa-2a combined with ribavirin has produced higher sustained virologic response rates (all HCV genotypes) than combined interferon alfa-2b/ribavirin in chronic hepatitis.
- Direct comparisons of peginterferon alfa-2b and peginterferon alfa-2a have not been performed. However, cross-comparison of studies suggests the similar efficacy of these agents with respect to sustained virologic response rates. Cost should be considered when selecting one over the other at present.
- From Bisceglie et al [Di Bisceglie AM, Hoofnagle JH. Optimal therapy of hepatitis C. Hepatology. 2002 Nov;36(5 Suppl 1):S121-7.] "The overall results from controlled trials suggest that they [both PEG INFs] achieve a similar rate of SVR (54% vs. 56% overall, 78 to 80% in genotype 2 and 3 and 42% to44% in genotype 1). While subgroup analyses may suggest superiority of one peg-interferon over the other, the post hoc analyses do not take into consideration the variability of patient populations treated and the different treatment regimens, particularly the dose of ribavirin. Furthermore, the greatest differences between the 2 pivotal trials of different forms of PEG INF were in the response rate to the standard interferon arm rather than in response rates to the peg-interferon regimens. Present data suggest that the peginterferon alpha 2-a and 2-b have similar efficacy in hepatitis C."
- According to the National Institutes of Health Consensus Development Conference: Management of Hepatitis C 2002: Both forms of pegylated interferon (alpha 2-a and alpha 2-b) appear to be similar in sustained viral response rates and efficacy when given with ribavirin. The size and branching of the PEG moiety appears to affect tissue distribution, metabolic pathway, and route of elimination of the parent compound. The improved responsiveness seen with the pegylated interferons is at least partially related to slower systemic clearance, which means peginterferon alfa-2a may have a theoretical advantage over peginterferon alfa -2b since it is cleared more slowly from the body.
- The IDEA trial (Individualized Dosing Efficacy vs. flat dosing to Assess optimal pegylated interferon therapy) sponsored by Schering-Plough (makers of PEG-Intron) is a planned study of 2,880 patients that will compare both pegylated forms of INF for the treatment of hepatitis C. This will be the first head to head trial initiated.
- Contraindications, warnings, adverse drug events, and drug interactions are similar for all pegylated interferon alpha products and are considered class effects. Refer to *Class Effects* table for more details.

Drug Class:	Pegylated Interferon Alpha Products

Summary of Indications

Chronic hepatitis C

Note: Peginterferon alfa-2a (Pegasys®) has been designated an orphan product for use in the treatment of renal cell carcinoma and chronic myelogenous leukemia

Place in Therapy

At present, either of these pegylated forms plus ribavirin should be considered the agent of choice in adult patients with compensated liver disease, particularly in patients with confirmed HCV genotype 1.

Department of Veterans Affairs Formulary

Interferon alfa-2b Inj/Ribavirin Oral

Summary of Pipeline Agents Expected to Offer Related Treatment Options

- **Infergen** (Amgen) - interferon alfacon-1 in combination with ribavirin for treatment of patients with chronic HCV who have failed to respond to therapy with pegylated interferon alpha 2 plus ribavirin (HCV nonresponders), daily dose of Infergen (vs the approved thrice-weekly dosing). Phase III DIRECT trial initiated 6/2004.
- ***Viramidine*** (Valeant Pharmaceuticals) - liver-targeting ribavirin prodrug/nucleoside (guanisine) analog in combination with pegylated interferon alpha for treatment of chronic HCV infection, oral formulation. Phase III VISER1 study initiated 12/2003; Phase III VISER2 study initiated 6/2004.
- ***Zadaxin*** (SciClone) - synthetically produced thymus hormone analogue/immunomodulator in combination with pegylated interferon alfa-2a (Roche's Pegasys) and a low dose of ribavirin as triple therapy for treatment of hepatitis C in patients who have not responded to prior therapy of interferon in combination with ribavirin Phase III in Europe planned for 4Q:2004, as of 5/2004. Zadaxin, Pegasys and ribavirin are approved in Mexico for hepatitis.
- **Merimepodib** (Vertex) is a small molecule, orally administered inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH). Recent reports in the medical literature suggest that IMPDH inhibitors such as merimepodib may enhance the antiviral activity of ribavirin in vitro by depleting GTP and increasing the rate of incorporation of ribavirin into viral RNA, rendering the virus nonfunctional. Merimepodib has been studied in combination with ribavirin and peginterferon. Phase IIb METRO trial initiated 7/2004.
- **NM-283** (Idenix Pharmaceuticals/Novartis) - nucleoside antiviral agent for treatment of infection by all HCV genotypes, including genotype I, once-daily oral administration, Phase I complete; Phase IIb planned by the end of 2004 (as of 8/2004)
- **Celgosivir** (Virogen/Migenix) - prodrug of castanospermine, a natural product derived from the Australian Black Bean chestnut tree/alpha glucosidase inhibitor for treatment of chronic hepatitis C virus (HCV) infection, oral formulation. Phase I/II complete. Phase IIa in Canada, as of 2004.
- **Albuferon** (human Genome Sciences) - long-acting form of recombinant interferon alpha/albumin fusion protein resulting from genetic fusion of human albumin and human interferon alpha, for treatment of chronic HCV infection Phase I/II completion in patients who have failed interferon alpha therapy expected in 2004; enrollment in Phase II trial in patients naive to interferon alpha treatment expected to conclude in 2004 (as of 4/2004)
- **SCV-07** (Vera Ltd/SciCLone) - second-generation immune system-enhancing immunomodulator that promotes differentiation of T-cells into the T helper 1 subset for treatment of HCV infection. Preclinical in the U.S.; IND filing planned (as of 8/2004).

Class Effects:	Pegylated Interferon Alpha Products
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Alpha-interferons induce various cellular activities related to binding with specific cell-surface membrane receptors; these include suppression of cell proliferation, antiviral activity, and immunomodulating effects, such as augmentation of macrophage phagocytic activity. They inhibit replication of hepatitis B and C viruses. Interferon alpha-2a and interferon alpha 2-b are a biosynthetic (recombinant DNA origin) form of interferon alpha that consists of 165 amino acids. Interferons alpha –2a and 2-b have molecular weights of approximately 19,000 daltons and differ at position 23 in the amino acid sequence, with alpha-2a possessing a lysine group and alpha-2b an arginine group at this position. The importance, if any of this single amino acid difference has yet to be established, and it remains to be elucidated whether clinically important differences in therapeutic/toxicologic profiles exist. **Pegylation**: Linkage with polyethylene glycol (pegylation) reduces the clearance of interferon alpha and may enhance its efficacy due to more prolonged exposure. Peginterferon alfa-2a is a pegylated form of interferon alfa-2a, synthesized by covalent attachment of a 40-kilodalton (kD) branched methoxy-polyethylene glycol moiety to the interferon alfa-2a molecule. Peginterferon alfa-2b is a covalent conjugate of straight-chain polyethylene glycol and recombinant interferon alfa-2b in a 1:1 ratio Pegylation of interferon alfa-2a confers protection against enzymatic degradation and reduces renal clearance, prolonging systemic exposure; in patients with hepatitis C, peginterferon alfa-2a can be administered once-weekly compared a three-times-weekly dosing requirement for interferon alfa-2a. Antiviral activity of peginterferon alfa-2a may be greater due to sustained therapeutic concentrations over one week, as opposed to fluctuations with interferon alfa-2a given three times weekly, enabling intermittent increases in viral load during treatment-free days The elimination half-life of peginterferon alfa-2b is up to 10-fold greater than that of nonpegylated interferon alfa-2b. Reduced renal elimination of peginterferon alfa-2b relative to nonpegylated interferon alfa-2b may be responsible for differences in the pharmacokinetics of these agents

Class Effects:	Pegylated Interferon Alpha Products
Pediatric Labeling	Safety and effectiveness in children less than 18 years has not been established
Contraindications	▪ Hypersensitivity ▪ Active autoimmune disease ▪ Decompensated liver disease ▪ Severe psychiatric disease
Major AEs / Warnings	Warnings: ▪ Psychiatric adverse events including depression and suicidal behavior have been associated with use. ▪ Rare cases of liver failure, cardiac arrhythmias, acute renal failure has occurred. ▪ Alpha Interferons can lead to abnormalities in thyroid functioning. ▪ Bone marrow toxicity has been associated with the use of alpha interferons. ▪ Pulmonary infiltrates, pneumonia and pneumonitis have occurred rarely. ▪ Retinal hemorrhages, cotton wool spots and retinal artery or vein obstruction have been observed rarely. ▪ Autoimmune diseases have been associated with alpha interferon therapy. Adverse Events: ▪ Influenza like symptoms, cognitive changes, injection site reactions, alopecia, and GI symptoms. ▪ The side-effect profile of both appears to be equal to that of the non-pegylated agents
Drug interactions	Theophylline: Reduced clearance of theophylline following coadministration. Neurotoxic, hematotoxic or cardiotoxic drugs: Effects of previously or coadministered drugs may be increased by interferons. Interleukin-2: Potential risk of renal failure. CNS drugs: Interactions could occur following coadministration of centrally acting drugs. Other interactions: Alfa-interferons may affect the oxidative metabolic process by reducing the activity of hepatic microsomal cytochrome enzymes in the P-450 group. Although the clinical relevance is still unclear, take into account when prescribing concomitant therapy with drugs metabolized by this route.
Key Populations	

Class Effects:	Pegylated Interferon Alpha Products
Renal Impairment	▪ Alpha-interferons are excreted renally. ▪ Monitoring for signs and symptoms of toxicity are indicated in all patients with mild to severe renal impairment. ▪ Empirical dose adjustments are indicated in individual patients with evidence of increased toxicity.
Pregnancy	Pregnancy Category C
Geriatric	Adverse effects may be more severe in elderly patients. Frequent monitoring for signs of toxicity is indicated in hepatitis C patients over 60 years of age, with empiric dose adjustments as deemed clinically necessary.
Race	No data

Drug Class:	Pegylated Interferon Alpha Products	
Characteristic	**Peginterferon alfa-2a**	**Peginterferon alfa-2b**
	Pegasys®	PEG-Intron®
Date of FDA Approval	January 22, 2001.	October 17, 2002.
Generic available?	No	
Manufacturer (if single source)	Roche	Schering-Plough
Dosage forms / route of admin	Solution for SQ injection: 180 µg/0.5 mL In single dose vials and single dose prefilled syringes. Also available co-packaged with ribavirin (180 µg/0.5 mL prefilled syringes co-packaged with Copegus tablets – 800 mg, 1000 mg or 1200 mg)	Powder for SQ injection available in kit containing: 2 dose vial, diluent, syringes and alcohol swabs. Powder for injection, lyophilized: 50mcg/0.5 mL when reconstituted. 80 mcg/0.5 mL when reconstituted. 120 mcg/0.5 mL when reconstituted. 150 mcg/0.5 mL when reconstituted. PEG-Intron Redipen PEG-interferon alfa 2b in pre-filled pen, 50, 80, 120 & 150 mcg new delivery system for PEG-interferon alfa consisting of active chamber containing Peg-Intron powder and diluent chamber containing sterile water in a disposable, single-use pen injection device
General dosing guidelines	180 mcg administered once weekly for 48 weeks. May reduce to 135 mcg if pt. Has a moderate or severe reaction. Further reduction to 90 mcg may be considered in severe reactions. Dosing is not based on weight	Administered once weekly based on weight ranges with dose being between 40 mcg and 150 mcg weekly.
FDA Labeled Indications	Chronic hepatitis C in patients not previously treated with interferon alfa, alone or with ribavirin	Chronic hepatitis C: For use alone or in combination with ribavirin capsules for the treatment of chronic hepatitis C in patients with compensated liver disease that have not been previously treated with interferon alpha and are at least 18 years of age.
Other Studied Uses	Peginterferon alfa-2a (Pegasys®) has been designated an orphan product for use in the treatment of renal cell carcinoma and chronic myelogenous leukemia	
Special Populations		

Drug Class:	Pegylated Interferon Alpha Products	
Characteristic	Peginterferon alfa-2a	Peginterferon alfa-2b
	Pegasys®	PEG-Intron®
Hepatic Impairment	The manufacturer recommends dose reduction to 135 µg in patients with progressive rises in ALT. Discontinuation of therapy is indicated if further ALT rises occur despite dose reduction, accompanied by increases in bilirubin, or evidence of hepatic decompensation	
Renal Impairment	▪ The manufacturer recommends dose reduction to 135 µg in patients with end-stage renal disease requiring hemodialysis. Clearance is reduced up to 45% in these patients ▪ Available data suggest no dose adjustment is indicated in patients with less severe forms of renal insufficiency.	▪ The clearance of peginterferon alfa-2b is reduced by approximately 50% in patients with a creatinine clearance of less than 50 mL/min indicating the need for dose reduction. However, specific guidelines are unavailable.
Geriatric	Pharmacokinetic data indicate similar pharmacokinetics of peginterferon alfa-2a in young and elderly (60 years or older) subjects.	One unpublished study reported no significant difference in peginterferon alfa-2b (single-dose) pharmacokinetics between elderly (over 65 years) and younger subjects This study was small, and renal function data were not provided.

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8. Product Information. Pegintron (peginterferon alfa-2b) Schering Corporation, Kenilworth, NJ (revised 10/2001) reviewed 10/2004.

Abstracts

Pharmacoeconomics. 2004;22(4):257-65.

Cost effectiveness of peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin as initial therapy for treatment-naive chronic hepatitis C.

Sullivan SD, Craxi A, Alberti A, Giuliani G, De Carli C, Wintfeld N, Patel KK, Green J.

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INTRODUCTION: In adults with previously untreated chronic hepatitis C (CHC), the combination of peginterferon alpha-2a plus ribavirin produces a higher rate of sustained virological response (SVR) than interferon alpha-2b plus ribavirin, but it is still unproven whether this increase is cost effective. The objective of this study was to determine if the gain in SVR with peginterferon alpha-2a plus ribavirin is worth the incremental cost. METHODS: We constructed a Markov model of disease progression in which cohorts of patients received peginterferon alpha-2a plus ribavirin or interferon alpha-2b plus ribavirin for 48 weeks (hepatitis C virus [HCV] genotype 1 and non-1 patients with fibrosis) or 24 weeks (genotype non-1 patients without fibrosis), and were followed for their expected lifetimes. The reference patient was a 45-year-old male with CHC without cirrhosis. The SVRs with peginterferon alpha-2a plus ribavirin and interferon alpha-2b plus ribavirin used to populate the model were 46% and 36% for patients infected with HCV genotype 1 and 76% and 61% for patients infected with HCV non-1 genotypes, respectively. QOL and costs for each health state were based on literature estimates and on Italian treatment patterns. Costs were in 2002 euros and benefits were discounted at 3%. Sensitivity analyses on key clinical and economic parameters were performed. The analysis was reported from the perspective of the Italian National Health Service. RESULTS: In patients infected with HCV genotype 1, peginterferon alpha-2a plus ribavirin increased life-years (LYs) by 0.78 years and QALYs by 0.67 years, compared with interferon alpha-2b and ribavirin. The incremental cost per LY and QALY gained was euro9433 and euro10 894, respectively. In patients infected with HCV non-1 genotypes, peginterferon alpha-2a plus ribavirin increased LYs by 1.17 and QALY by 1.01 years, compared with interferon alpha-2b plus ribavirin. The incremental cost per LY and QALY gained was euro3261 and euro3766, respectively. Using genotype distribution estimates, the weighted average ICER for all genotypes was euro6811 per LY gained and euro7865 per QALY gained. CONCLUSION: Our model suggests that peginterferon alpha-2a plus ribavirin is cost effective compared with conventional interferon alpha-2b plus ribavirin for treatment of naive adults with CHC, regardless of HCV genotype, under a wide range of assumptions regarding treatment effectiveness and costs.

Pegylated interferon with ribavirin therapy for chronic infection with the hepatitis C virus.

Expert Opin Pharmacother. 2003 May;4(5):685-91

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Chronic infection with the hepatitis C virus is common. In the past, therapy involved a combination of thrice-weekly interferon (IFN) injections combined with oral ribavirin. This therapy was expensive, poorly tolerated and poorly effective, only curing approximately 40% of treated patients. Long-acting IFNs have recently been developed by linking IFN to polyethylene glycol and these 'pegylated' IFNs are now the standard of care for patients with chronic hepatitis C (CHC).

Two pegylated (PEG) IFNs are available; 40 kDa PEG-IFNalpha(2a) (Pegasys, Hoffmann-La Roche) and the 12 kDa PEG-IFN-alpha(2b) (Peg-Intron, Schering-Plough). They have different physicochemical, pharmacokinetic and pharmacodynamic properties. The 40 kDa PEG-IFN-alpha(2a) is dispensed as a solution and used at a fixed dose whereas the 12 kDa PEG-IFN-alpha(2b) is a dry powder, which is reconstituted prior to administration, and the dose is dependent upon body weight.

Both PEG-IFNs are given by a once-weekly injection and as monotherapy, they are more effective than standard IFN-alpha. The 40 kDa PEGIFN-alpha(2a) cures 36 - 39% of patients and the 12 kDa pegylated-IFN-alpha(2b) cures 23 - 25%. When combined with ribavirin, the two PEG-IFNs have acceptable safety profiles and cure > 50% of treated patients (56 and 54% for the 40 kDa PEG-IFN-alpha(2a) and 12 kDa PEG-IFN-alpha(2b), respectively). For the 40 kDa PEG-IFN-alpha(2a) it is possible to predict the outcome of therapy after 12 weeks of treatment.

The new PEG-IFNs are a significant advance in the therapy of CHC infection. Their ease of administration, coupled with their improved efficacy, is likely to lead to an increase in the proportion of infected patients who wish to receive treatment.

Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial.

Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK.

Lancet. 2001 Sep 22;358(9286):958-65.

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BACKGROUND: A sustained virological response (SVR) rate of 41% has been achieved with interferon alfa-2b plus ribavirin therapy of chronic hepatitis C. In this randomised trial, peginterferon alfa-2b plus ribavirin was compared with interferon alfa-2b plus ribavirin.

METHODS: 1530 patients with chronic hepatitis C were assigned interferon alfa-2b (3 MU subcutaneously three times per week) plus ribavirin 1000-1200 mg/day orally, peginterferon alfa-2b 1.5 microg/kg each week plus 800 mg/day ribavirin, or peginterferon alfa-2b 1.5 microg/kg per week for 4 weeks then 0.5 microg/kg per week plus ribavirin 1000-1200 mg/day for 48 weeks. The primary endpoint was the SVR rate (undetectable hepatitis C virus [HCV] RNA in serum at 24-week follow-up). Analyses were based on patients who received at least one dose of study medication.

FINDINGS: The SVR rate was significantly higher (p=0.01 for both comparisons) in the higher-dose peginterferon group (274/511 [54%]) than in the lower-dose peginterferon (244/514 [47%]) or interferon (235/505 [47%]) groups. Among patients with HCV genotype 1 infection, the corresponding SVR rates were 42% (145/348), 34% (118/349), and 33% (114/343). The rate for patients with genotype 2 and 3 infections was about 80% for all treatment groups. Secondary analyses identified bodyweight as an important predictor of SVR, prompting comparison of the interferon regimens after adjusting ribavirin for bodyweight (mg/kg). Side-effect profiles were similar between the treatment groups.

INTERPRETATION: In patients with chronic hepatitis C, the most effective therapy is the combination of peginterferon alfa-2b 1.5 microg/kg per week plus ribavirin. The benefit is mostly achieved in patients with HCV genotype 1 infections.

Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.

Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J.

N Engl J Med. 2002 Sep 26;347(13):975-82

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BACKGROUND: Treatment with peginterferon alfa-2a alone produces significantly higher sustained virologic responses than treatment with interferon alfa-2a alone in patients with chronic hepatitis C virus (HCV) infection. We compared the efficacy and safety of peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, and peginterferon alfa-2a alone in the initial treatment of chronic hepatitis C.

METHODS: A total of 1121 patients were randomly assigned to treatment and received at least one dose of study medication, consisting of 180 microg of peginterferon alfa-2a once weekly plus daily ribavirin (1000 or 1200 mg, depending on body weight), weekly peginterferon alfa-2a plus daily placebo, or 3 million units of interferon alfa-2b thrice weekly plus daily ribavirin for 48 weeks.

RESULTS: A significantly higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) than of patients who received interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, P<0.001) or peginterferon alfa-2a alone (56 percent vs. 29 percent, P<0.001). The proportions of patients with HCV genotype 1 who had sustained virologic responses were 46 percent, 36 percent, and 21 percent, respectively, for the three regimens. Among patients with HCV genotype 1 and high base-line levels of HCV RNA, the proportions of those with sustained virologic responses were 41 percent, 33 percent, and 13 percent, respectively. The overall safety profiles of the three treatment regimens were similar; the incidence of influenza-like symptoms and depression was lower in the groups receiving peginterferon alfa-2a than in the group receiving interferon alfa-2b plus ribavirin.

CONCLUSIONS: In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone.

Pegylated interferons for the treatment of chronic hepatitis C infection

Luxon BA, Grace M, Brassard D, Bordens R.

Clin Ther. 2002 Sep;24(9):1363-83.

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BACKGROUND: Interferon (IFN) alfa is a clinically effective therapy used in a wide range of viral infections and cell-proliferative disorders. Combination therapy with IFN alfa-2b and ribavirin is the current standard of care for the treatment of chronic hepatitis C (CHC) infection. However, standard IFN alfa has the drawbacks of a short serum half-life and rapid clearance. To overcome this problem, 2 pegylated forms of IFN have been developed and tested clinically.

OBJECTIVE: This article reviews the development and properties of pegylated IFN alfa-2b and pegylated IFN alfa-2a, and presents safety and efficacy data from recent clinical trials.
METHODS: Relevant clinical studies were identified through a MEDLINE search from 1966 through the present using the key words hepatitis C and interferon. Studies of the pegylated IFNs in humans were then selected.

RESULTS: Pegylated IFN alfa-2b is formed by covalent conjugation of a 12-kd mono-methoxy polyethylene glycol (PEG) molecule to IFN alfa-2b, and pegylated IFN alfa-2a by covalent conjugation of a 40-kd branched mono-methoxy PEG molecule to IFN alfa-2a. The 2 pegylated IFNs differ in the mixture of pegylation isomers resulting from their conjugation chemistry. Pegylated IFN alfa-2b has a prolonged serum half-life (40 hours) relative to standard IFN alfa-2b (7-9 hours). The greater polymer size of pegylated IFN alfa-2a acts to reduce glomerular filtration, markedly prolonging its serum half-life (72-96 hours) compared with standard IFN alfa-2a (6-9 hours). In clinical studies, once-weekly dosing of the pegylated IFNs was associated with a sustained virologic response in patients infected with hepatitis C virus (HCV). Once-weekly dosing with either of the pegylated IFNs was more effective than the respective thrice-weekly regimen of IFN alfa, with a comparable safety profile. The combination of once-weekly pegylated IFN and ribavirin effectively reduced HCV viral load and sustained viral suppression.

CONCLUSIONS: Once-weekly dosing with either pegylated IFN alfa-2b or pegylated IFN alfa-2a has been shown to produce significantly higher rates of viral eradication than standard thrice-weekly IFN alfa therapy without compromising safety. With respect to the treatment of CHC, the greatest anti-HCV efficacy has been achieved with the combination of once-weekly pegylated IFN and ribavirin.

Pegylated interferons.

Karnam US, Reddy KR.

Clin Liver Dis. 2003 Feb;7(1):139-48.

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In summary, pegylated IFNs have a longer half-life, reduced immunogenicity, better pharmacokinetics, and enhanced biological activity when compared with standard IFN. Better adherence rates are feasible because of the once weekly administration of pegylated IFN. The adverse event profile is largely comparable. The improved pharmacokinetics of pegylated IFNs, compared with standard IFN, has translated into greater efficacy with at least similar tolerability. Pegylated IFNs with ribavirin are the standard of care for treating patients with chronic HCV who have not been treated previously.

Clinical trial results of peginterferons in combination with ribavirin.

Craxi A, Licata A.

Semin Liver Dis. 2003;23 Suppl 1:35-46.

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Of the large number of patients chronically infected with hepatitis C virus (HCV), only about one third have progressive liver disease, and will eventually develop cirrhosis and hepatocellular carcinoma. These are the patients for whom effective antiviral treatment is most needed. Therapy is currently recommended for patients with chronic hepatitis C who have abnormal alanine aminotransferase (ALT) levels, detectable hepatitis C virus ribonucleic acid (HCV RNA) in the blood, and significant necroinflammatory changes and/or fibrosis on liver biopsy.

The current gold standard in terms of treatment efficacy is the combination of peginterferon (PEG-IFN) and ribavirin. The overall sustained virological response rate (SVR) with these regimens is 54 to 61% following 48 weeks of therapy. Patients with genotype 1 infection have a 42 to 51% likelihood of response to 48 weeks of therapy. Those with genotypes 2 or 3 infection will respond to 24 weeks of therapy in 78 to 82% of cases. These SVR rates are 5 to 10 percentage points higher in all patient groups than in those obtained with standard doses of interferon (IFN) and ribavirin. Retreatment of nonresponders to standard IFN monotherapy using PEG-IFN and ribavirin has achieved SVR rates of 34 to 40%. Retreatment of patients who relapsed after IFN monotherapy has resulted in an SVR rate of about 60%.

A SVR after retreatment of relapsers and nonresponders with PEG-IFN and ribavirin is more likely in patients previously treated with IFN monotherapy, those with HCV genotypes 2 or 3, patients with low viral load (<2 million copies/mL), and individuals who had a significant decrease in HCV RNA levels during the initial treatment. The potential benefits of long-term anti-HCV suppressive therapy in nonresponders are currently under investigation.

Hepatology. 2002 Nov;36(5 Suppl 1):S121-7.

Optimal therapy of hepatitis C.

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The highest response rates to antiviral therapy for the treatment of chronic hepatitis C have been achieved using the combination of peginterferon and ribavirin. Recently completed controlled trials have reported rates of sustained virological response (SVR) between 50% and 60% in patients treated with higher doses of peginterferon and ribavirin, which was 5% to 10% higher with standard doses of interferon alfa and ribavirin. The major determinant of outcome of therapy is hepatitis C virus (HCV) genotype. With the combination of peginterferon and ribavirin, patients with genotype 1 achieve response rates of 40% to 45%, compared with rates approaching 80% with genotypes 2 or 3. Importantly, patients with HCV genotype 1 achieve higher rates of response with 48 weeks than with 24 weeks of therapy, whereas patients with genotypes 2 and 3 are adequately treated with a 24-week course. Furthermore, patients with genotypes 2 and 3 require only 800 mg of ribavirin daily to achieve optimal response rates, whereas 1,000 to 1,200 mg daily is needed for patients with genotype 1. Future studies should focus on optimizing the dose of peginterferon and ribavirin by patient characteristics, particularly on resolving the issue of weight-based dosing. For patients with good prognostic factors, a lower dose and shorter course of peginterferon may be adequate for full effect. Importantly, research is needed to show how treatment regimens can best be applied to other patient groups with hepatitis C, such as patients with acute hepatitis, human immunodeficiency virus coinfection, renal disease, solid-organ transplant, neuropyschiatric disease, autoimmunity, and alcohol or substance abuse.

Drug Class:	Ribavirin	
Drugs Reviewed:	Ribavirin (Rebetol®)	Ribavirin (Copegus®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently two ribavirin products available in the United States as indicated above. They contain the same drug, one as a capsule and one as a tablet.
- The difference in labeling for these two products (same drug) is due to the interferon that they are paired with for the treatment of hepatitis C infections. The tablets (Copegus®, Roche) are paired with peginterferon alfa-2a (Pegasys®, Roche), while the capsules (Rebetol®, Schering-Plough) are paired with interferon alfa-2b (Intron-A®, Schering-Plough).
- The safety and efficacy of ribavirin capsules with interferons other than interferon alfa-2b or peginterferon alfa-2a products have not been established.
- Since the two products contain the same drug, contraindications, warnings, adverse drug events, and drug interactions are identical for both drugs. Refer to *Class Effects* table for more details.

Summary of Indications

Copegus® Tablets: In combination with peginterferon alfa-2a for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

Rebetol® Capsules and oral solution: In combination with Intron A (interferon alfa-2b) injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

Rebetol® Capsules: In combination with Peg-Intron (peginterferon alfa-2b) injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

Place in Therapy

- Ribavirin plus interferon alfa is the standard of care for the treatment of chronic hepatitis C. Ribavirin is never used alone but always in combination with interferon alfa or peginterferon alfa. The two available oral ribavirins (Rebetrol® and Copegus®) are considered clinically equivalent.
- Hepatitis C virus (HCV) infection can lead to chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Nearly 4 million Americans are infected with hepatitis C which accounts for 8,000 to 10,000 deaths annually. The number one reason for liver transplantation in the United States is infection with HCV.
- Ribavirin has a broad spectrum of antiviral activity, with documented efficacy in the treatment of influenza A and B. The efficacy of ribavirin in treating respiratory syncytial virus (RSV) infections is controversial. Ribavirin aerosol therapy may be considered in infants and young children who are at high risk for serious respiratory syncytial virus infection.
- The Working Group on Civilian Biodefense recommends the use of ribavirin for the treatment of hemorrhagic fever of unknown etiology or secondary to Arenaviruses or Bunyaviruses in the event these viruses are used as a biological

weapon. Intravenous ribavirin is recommended in a contained casualty situation and oral ribavirin is recommended in a mass casualty situation (a high number of casualties making intravenous therapy impossible).

Department of Veterans Affairs Formulary

Interferon alfa-2b Inj/Ribavirin Oral
Ribavirin Oral

Summary of Pipeline Agents Expected to Offer Related Treatment Options

- **Infergen** (Amgen) - interferon alfacon-1 in combination with ribavirin for treatment of patients with chronic HCV who have failed to respond to therapy with pegylated interferon alpha 2 plus ribavirin (HCV nonresponders), daily dose of Infergen (vs the approved thrice-weekly dosing). Phase III DIRECT trial initiated 6/2004.
- **Viramidine** (Valeant Pharmaceuticals) - liver-targeting ribavirin prodrug/nucleoside (guanisine) analog in combination with pegylated interferon alpha for treatment of chronic HCV infection, oral formulation. Phase III VISER1 study initiated 12/2003; Phase III VISER2 study initiated 6/2004.
- ***Zadaxin*** (SciClone) - synthetically produced thymus hormone analogue/immunomodulator in combination with pegylated interferon alfa-2a (Roche's Pegasys) and a low dose of ribavirin as triple therapy for treatment of hepatitis C in patients who have not responded to prior therapy of interferon in combination with ribavirin Phase III in Europe planned for 4Q:2004, as of 5/2004. Zadaxin, Pegasys and ribavirin are approved in Mexico for hepatitis.
- **Merimepodib** (Vertex) is a small molecule, orally administered inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH). Recent reports in the medical literature suggest that IMPDH inhibitors such as merimepodib may enhance the antiviral activity of ribavirin in vitro by depleting GTP and increasing the rate of incorporation of ribavirin into viral RNA, rendering the virus nonfunctional. Merimepodib has been studied in combination with ribavirin and peginterferon. Phase IIb METRO trial initiated 7/2004.
- **NM-283** (Idenix Pharmaceuticals/Novartis) - nucleoside antiviral agent for treatment of infection by all HCV genotypes, including genotype I, once-daily oral administration, Phase I complete; Phase IIb planned by the end of 2004 (as of 8/2004)
- **Celgosivir** (Virogen/Migenix) - prodrug of castanospermine, a natural product derived from the Australian Black Bean chestnut tree/alpha glucosidase inhibitor for treatment of chronic hepatitis C virus (HCV) infection, oral formulation. Phase I/II complete. Phase IIa in Canada, as of 2004.
- **Albuferon** (human Genome Sciences) - long-acting form of recombinant interferon alpha/albumin fusion protein resulting from genetic fusion of human albumin and human interferon alpha, for treatment of chronic HCV infection Phase I/II completion in patients who have failed interferon alpha therapy expected in 2004; enrollment in Phase II trial in patients naive to interferon alpha treatment expected to conclude in 2004 (as of 4/2004)
- **SCV-07** (Vera Ltd/SciCLone) - second-generation immune system-enhancing immunomodulator that promotes differentiation of T-cells into the T helper 1 subset for treatment of HCV infection. Preclinical in the U.S.; IND filing planned (as of 8/2004).

Class Effects:	Ribaviran
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	▪ Ribavirin is a synthetic nucleoside analog, consisting of D-ribose attached to a 1,2,4 triazole carboxamide. The drug has a wide spectrum of antiviral activity in vitro against both RNA and DNA viruses. The drug is readily transported into cells and then converted by cellular enzymes to 5-mono-, di-, and triphosphate derivatives, which are responsible for inhibiting certain viral enzymes involved in viral nucleic acid synthesis. ▪ Ribavirin produces its antiviral effect primarily by altering the nucleotide pools and normal messenger RNA formation, which could account for its effectiveness against both DNA and RNA viruses. The monophosphate is an inhibitor of inosine monophosphate dehydrogenase which is involved in the synthesis of guanosine monophosphate. **Spectrum Of Activity:** In general, the in vitro activity of the drug against herpes simplex is comparable to that of vidarabine or idoxuridine. Similar activity to amantadine against influenza A virus has been reported. However, ribavirin is more active than vidarabine or idoxuridine against other DNA viruses and has activity against many RNA and DNA viruses unresponsive to presently available antiviral agents. ▪ DNA viruses which are most sensitive to ribavirin in vitro include herpes simplex, pox viruses (vaccinia and myxoma), and Marek's disease virus. DNA viruses which are insensitive to ribavirin include varicella, pseudorabies, infectious bovine, and rhinotracheitis. ▪ Susceptible RNA viruses include influenza A and B paramyxovirus (parainfluenza, measle, mumps, and Newcastle disease viruses), reoviruses, and some rhinoviruses, and RNA tumor viruses. Insensitive RNA viruses in vitro include the enterovirus, rhinovirus 2, 42, and Semliki Forest virus. ▪ The in vivo antiviral spectrum of the drug is narrower than that observed in vitro. In vivo activity depends upon numerous factors including virus strain, dosage, route of infection, age and sex of animals tested, timing, and route of drug administration. ▪ Animal studies have shown in vivo activity against herpes simplex Type 1 and 2 (reduction in lesions), vaccinia (lesions reduced), Lassa fever (reduction in viremia and increased survival), influenza A and B (increased survival), parainfluenza (increased survival), and yellow fever (increased survival). The drug essentially had no effect in vivo against cytomegalovirus, hepatitis B, polio viruses, or rotavirus.
Contraindications	▪ Autoimmune hepatitis ▪ Hypersensitivity ▪ Decompensated liver disease ▪ Pregnancy or male partner of pregnant female ▪ Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia)
Major Adverse Effects / Warnings	▪ Do not use alone in the treatment of chronic hepatitis C virus infection as monotherapy is not effective. ▪ Primary toxicity is hemolytic anemia (which was observed in approximately 10% of patients in clinical trials) - labs at initiation, 2 and 4 weeks and then as clinically appropriate. Cardiac and pulmonary events associated with anemia occurred in

Class Effects:	Ribaviran
	approximately 10% of patients. ▪ The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. ▪ Side effects associated with combination therapy: influenza like symptoms, cognitive changes, alopecia, and gastrointestinal (GI) symptoms. ▪ Ribavirin/interferon combination is associated with an increase in GI symptoms, dyspnea, rash, and pruritus in comparison to interferon alpha alone. ▪ Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up ▪ Therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. ▪ Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with ribavirin/interferon therapy; occasional cases of fatal pneumonia have occurred.
Drug interactions	▪ Didanosine ▪ Stavudine ▪ Zidovudine
Pharmacokinetic Issues	Both the area under the curve (AUC) and peak serum concentration (C_{max}) increased by 70% when ribavirin capsules (Rebetol®) were administered with a high-fat meal. For ribavirin tablets (Copegus®), the absorption was slowed (time to maximum concentration was doubled) and the AUC and C_{max} increased by 42% and 66%, respectively, when taken with a high-fat meal. There is insufficient data to address the clinical relevance of these results.
Special Populations	
Hepatic Impairment	The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.
Renal Impairment	Patients with a creatinine clearance <50 mL/min should not be treated with ribavirin.
Pregnancy	**FDA Category X** Teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days which may persist in nonplasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-

Class Effects:	Ribaviran
	up period.
Geriatric	Ribavirin should be initiated cautiously in elderly patients, starting with the lower dosing range. Elderly individuals had a higher frequency of anemia (67%) than younger individuals (28%) in clinical trials.
Race	Insufficient non-Caucasian subjects studied to adequately determine potential pharmacokinetic differences between populations. Treatment response rates with Peg-Intron/Rebetol were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Drug Class:	Ribavirin	
Characteristic	**Rebetol®**	**Copegus®**
Date of FDA Approval	Capsules: June 3, 1998 40mg/ml solution: July 31, 2003	December 3, 2002
Generic available?	Yes – capsules No - solution	No
Manufacturer (if single source)	Schering-Plough	Roche
Dosage forms / route of administration	Capsules: 200 mg Oral Solution: 40mg/ml	Tablets: 200 mg
Dosing frequency	BID	
General dosing guidelines	The recommended dose of Rebetrol capsules is 1000 -1200 mg/day based on the patient's body weight. ▪ 75 mg – 1200 mg in two divided doses, ▪ = 75 kg – 1000 mg in two divided doses Pediatric dosing - The recommended dose of REBETOL is 15 mg/kg per day in two divided doses Rebetrol may be administered without regard to food, but should be administered in a consistent manner with respect to food intake.	Range of 800-1200 mg/day. Dosed based on weight, disease characteristics (genotype), and patient tolerability. Genotype 1, 4 – ▪ = 75 mg – 1200 mg in two divided doses, ▪ < 75 kg – 1000 mg in two divided doses Genotype 2,3 – 800 mg in two divided doses The manufacturer recommends Copegus should be administered with food. Also available co-packaged with PEG-Intron - 180 µg/0.5 mL prefilled syringes co-packaged with Copegus tablets – 800 mg, 1000 mg or 1200 mg
Pediatric Labeling	Rebetol® capsules, in combination with Intron A® (interferon alfa 2-b, recombinant), are indicated in the treatment of chronic hepatitis C in patients five years and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy. The oral solution has the same indication for children three years of age and older.	Safety and effectiveness of Copegus® have not been determined in patients < 18 years of age.

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Abstracts

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Peginterferon-alpha-2a (40kD) plus ribavirin: a review of its use in the management of chronic hepatitis C.

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Pegylation of interferon-alpha-2a is associated with improved sustained virological response rates in patients with chronic hepatitis C. Subsequently, combination therapy with peginterferon-alpha-2a (40kD) [Pegasys] and ribavirin (Copegus trade mark, Rebetol) was investigated to establish if the efficacy of peginterferon-alpha-2a (40kD) monotherapy could be further enhanced. Subcutaneous peginterferon-alpha-2a (40kD) was administered at a dosage of 180 micro g once weekly and oral ribavirin was usually administered at a dosage of 1000 or 1200 mg/day. In treatment-naive patients with chronic hepatitis C, the sustained virological response rate (assessed 24 weeks after the end of a 48-week treatment period) was significantly higher in peginterferon-alpha-2a (40kD) plus ribavirin recipients than in peginterferon-alpha-2a (40kD) plus placebo recipients or interferon-alpha-2b plus ribavirin recipients (56% vs 29% and 44%). Retrospective analysis revealed that peginterferon-alpha-2a (40kD) plus ribavirin recipients who did not achieve an early virological response were unlikely to achieve a sustained response. Treatment with peginterferon-alpha-2a (40kD) plus another antiviral agent (ribavirin, mycophenolate mofetil, amantadine, or ribavirin and amantadine) was beneficial in patients with chronic hepatitis C who had relapsed during or after, or had not responded to, treatment with interferon-alpha-2b plus ribavirin. In the relapse study, sustained virological response rates in recipients of peginterferon-alpha-2a (40kD) plus ribavirin were 45% with and 38% without amantadine. Peginterferon-alpha-2a (40kD) plus ribavirin appears beneficial in patients with chronic hepatitis C considered difficult to treat (e.g. patients infected with hepatitis C virus genotype 4, African-American patients, patients with advanced fibrosis or cirrhosis and patients co-infected with HIV). Flu-like symptoms and depression occurred significantly less frequently with peginterferon-alpha-2a (40kD) plus ribavirin than with interferon-alpha-2b plus ribavirin. Similar proportions of patients receiving peginterferon-alpha-2a (40kD) plus ribavirin, peginterferon-alpha-2a (40kD) plus placebo and interferon-alpha-2b plus ribavirin withdrew from treatment because of laboratory abnormalities or other adverse events. In conclusion, combination therapy comprising subcutaneous peginterferon-alpha-2a (40kD) and oral ribavirin is an important new treatment option for chronic hepatitis C. Peginterferon-alpha-2a (40kD) plus oral ribavirin is significantly more effective than peginterferon-alpha-2a (40kD) monotherapy or interferon-alpha-2b plus ribavirin at inducing a sustained virological response in treatment-naive patients with chronic hepatitis C. Preliminary data suggest that peginterferon-alpha-2a (40kD) plus ribavirin is also beneficial in treatment-experienced patients and in patients who have traditionally been considered difficult to treat. Combination therapy with peginterferon-

alpha-2a (40kD) and oral ribavirin is poised to become a valuable first-line treatment option in chronic hepatitis C.

J Clin Pharmacol. 1989 Dec;29(12):1128-34.

Comparison of oral and aerosol ribavirin regimens in the high risk elderly.

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A comparison of different regiments of ribavirin (R), administered either orally or by aerosol, was performed in 16 elderly subjects (13 men, 3 women, mean age 63 +/- 8 years) considered to be in the "high-risk" category for complications from influenza as defined by the Centers for Disease Control. The subjects were divided into four groups. Group O-600 received 600 mg orally R every 8 hours for 48 hours followed by 200 mg every 8 hours for 72 hours for a total dose of 5.4 g (22.1 mmol). Group O-800 received 800 mg oral R every 8 hours for 24 hours followed by 400 mg every 12 hours for 96 hours for a total dose of 4.1 g (22.9 mMoles). Group A-40 received R (40 mg/ml) aerosolized through a small particle aerosol generator for 6 hours every 12 hours for 96 hours, yielding an average delivered dose of 6.2 g (25.4 mMoles) R. Group A-60 received aerosolized R (60 mg/mL) for 2 hours every 8 hours for 96 hours, yielding an average delivered dose of 4.6 g (18.8 mMoles) R. No hematologic or other laboratory abnormalities were associated with any of the regimens. Group O-800 and O-600 reached mean peak plasma R levels of 11.8 microM and 5.3 microM, respectively, after 18 hours of therapy. Subsequent administration of 20 mg R every 8 hours was sufficient to maintain a plasma R level greater than 7 microM. Among the aerosol groups, group A-40 approached steady state plasma R levels (8-10 microM) more quickly than group A-60.

Clin Pharmacol Ther. 1991 Oct;50(4):442-9.

Pharmacokinetics and long-term tolerance to ribavirin in asymptomatic patients infected with human immunodeficiency virus.

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Single-dose and steady-state pharmacokinetics of the antiviral agent ribavirin were studied in seven male, asymptomatic, human immunodeficiency virus-seropositive subjects. After a single 400 mg intravenous infusion, mean terminal plasma half-life (t1/2) was 27.1 hours, mean volume of distribution was 802 L, and mean total plasma clearance was 26.1 L/hr. Renal clearance was 39% of total clearance and it exceeded creatinine clearance. Oral bioavailability was 44.6%. With long-term dosing (400 mg orally twice a day) ribavirin accumulated, reaching steady state in 2 to 4 weeks in plasma and red blood cells. Red blood cell concentrations greatly exceeded plasma concentrations (60:1). Plasma concentrations at steady state (trough) were 10- to 14-fold higher than the corresponding single-dose concentrations. The terminal t1/2 (washout) after 16 weeks greatly exceeded the t1/2 observed after a single oral dose (151 versus 29.6 hours). Ribavirin-induced reductions in hemoglobin ranging from 0.8 to 3.5 gm/dl were well tolerated. There was no significant reduction in CD4 lymphocytes during treatment with ribavirin for 16 weeks in subjects who had more than 200 CD4 cells at entry and who also remained free of opportunistic infections during 24 weeks of observation.

Antimicrob Agents Chemother. 1999 Oct;43(10):2451-6.

Pharmacokinetics and absolute bioavailability of ribavirin in healthy volunteers as determined by stable-isotope methodology.

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Ribavirin has recently been demonstrated to have efficacy in combination with alpha interferon for treatment of relapsed hepatitis C. The marked improvement in the response rate after treatment with the combination regimen (10-fold higher versus that from monotherapy with alpha interferon) highlights the importance of determining the absolute bioavailability of ribavirin as a first step in beginning to investigate the pharmacodynamics of the combination. The objective of this study was to determine the absolute bioavailability of ribavirin with an intravenous formulation containing ribavirin labeled with the stable isotope (13)C(3) ((13)C(3)-ribavirin) and unlabeled oral ribavirin. Six healthy volunteers received 150 mg of intravenous (13)C(3)-ribavirin followed 1 h later by a 400-mg oral dose of ribavirin. Samples of blood and urine were collected up to 169 h postdosing. Concentrations of (13)C(3)-ribavirin and unlabeled ribavirin were determined by a high-performance liquid chromatography tandem mass spectrometric method. All plasma and urine data were comodeled for labeled and unlabeled ribavirin by using both the two- and three-compartment models in the program ADAPT II. A three-compartment model was chosen for the pharmacokinetic analysis with the Akaike Information Criterion. The mean maximum concentrations of drug in plasma for intravenous and oral ribavirin were 4,187 and 638 ng/ml, respectively. The mean bioavailability was 51.8% +/- 21.8%, and the mean gamma-phase half-life was 37.0 +/- 14. 2 h. The mean renal clearance, metabolic clearance, and volume of distribution of the central compartment were 6.94 liters/h, 18.1 liters/h, and 17.8 liters, respectively. The use of the stable-isotope methodology has provided the best estimate of the absolute bioavailability of ribavirin that is currently available, as there was neither a period bias nor a washout effect to confound the data. The study demonstrated that the mean bioavailability for a 400-mg dose of ribavirin was 52%, which is higher than that previously reported in other investigations.

Drug Class:	Short-Acting Beta-2 Agonists: Oral Inhalation & Nebulized		
Inhalers:	albuterol (Proventil®, Ventolin®)	metaproterenol (Alupent®)	pirbuterol (Maxair Autohaler®)
Nebulized:	albuterol (AccuNeb®, Proventil®)	metaproterenol (Alupent®)	levalbuterol (Xopenex®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently four short-acting beta-2 agonists for inhalation available in the United States as indicated above. Two (albuterol, and metaproterenol) are available as both metered dose inhalers (MDI) and nebulized solutions. Pirbuterol is available as a MDI, while levalbuterol is currently only available as a nebulized solution. A MDI version of levalbuterol is in Phase III clinical trials.
- There are currently 4 FDA approved indications for one or more of the short-acting beta-2 agonists (see *Indications Table* that follows).
- All of the short-acting beta-2 agonists are FDA approved for treatment of bronchospasm.
- All of the inhaled short-acting beta-2 agonists are relatively selective for $ß_2$ receptors, although all have minor $ß_1$ activity. Most clinical studies do not show clinically significant $ß_1$ effects with any of the inhaled agents.
- Based on in vitro results, the following are listed from most to least potent: isoproterenol > albuterol > metaproterenol > pirbuterol.
- Levalbuterol provides a reasonable treatment alternative for patients in whom albuterol, or another beta-2 agonist, is effective but who experience significant adverse effects. However, many patients with asthma are maintained effectively with racemic albuterol and switching to levalbuterol may not be necessary, especially if the cost of the latter is significantly higher.
- Ahrens and Weinberger concluded (abstract attached): "Considering the greater cost that is currently associated with Xopenex, routine use of this product has the potential to increase the cost of asthma care without identified benefit."

Efficacy

- Albuterol compares favorably to isoproterenol, metaproterenol, terbutaline, and fenoterol in efficacy and safety as a bronchodilator. Albuterol is considered to be one of the beta-agonists of choice for initiation of bronchodilator therapy.
- In a single-blind cross-over study, 12 asthmatics received single doses of pirbuterol 200 and 400 micrograms (mcg), albuterol 200 mcg, and placebo aerosols in randomized order (Beumer, 1979). No significant differences were found between albuterol 200 mcg and pirbuterol 400 mcg when lung functions were studied over 4 hours following inhalation. Pirbuterol 400 mcg and albuterol 200 mcg were significantly better than pirbuterol 200 mcg. No significant changes in pulse rate, blood pressure or EKG were noted for either drug.

Adverse Events

- Contraindications, warnings, adverse drug events, and drug interactions are similar for all short-acting beta-2 agonists and are considered class effects. Refer to Class Effects table for more details.
- Eight centers conducted a blinded 12 week study on 133 patients with asthma to measure incidence and types of side effects and tolerance to bronchodilation from prolonged use of aerosol bronchodilators. Metaproterenol 1.3 mg four times daily, pirbuterol 0.4 mg four times daily, and placebo multidose inhalers were used by all subjects. Sixty-six patients (28 male & 38 female) received pirbuterol and 67 (30 male & 37 female) received metaproterenol. Ages of patients spanned from 18 to 73 years. Tolerance to drug effect for both drugs could not be demonstrated. A difference in incidence of side effects also could not be demonstrated between metaproterenol and pirbuterol. The

most common side effects were (pirbuterol/metaproterenol): nervousness (14/7), nausea (4/1), headache (3/3), tremors (3/2), tachycardia (2/2), and dry mouth (1/1) (Tinkelman et al, 1990).

- Levalbuterol is the R(-)-enantiomer of racemic albuterol. All the bronchodilating activity of commercially-available racemic albuterol resides in this isomer, which is the active beta-2 receptor agonist. The S(+)-enantiomer does not bind to beta-2 adrenoceptors, but may be responsible for some adverse effects of racemic albuterol, including bronchial hyperreactivity and reduced pulmonary function during prolonged use.

Summary of Indications

FDA labeled Indications	albuterol Proventil® Ventolin® AccuNeb®	metaproterenol Alupent®	pirbuterol Maxair®	levalbuterol Xopenex®
Treatment of bronchial asthma	C	✓	C	C
Prevention of bronchospasm	✓	C	✓	✓
Treatment of bronchospasm	✓	✓	✓	✓
Prevention of exercise induced bronchospasm.	✓	C	C	C

✓ = FDA approved indication C = Not FDA approved; however, studies indicate class effect

Place in Therapy

Availability of an inhaled short-acting beta-2 agonist such as inhaled albuterol is recommended for all asthma patients. Short-acting inhaled beta-2 agonists may be useful for intermittent episodes of asthma, and to prevent exercise-induced asthma. Oral beta-2 agonists have a limited place in chronic asthma management.

Department of Veterans Affairs Formulary

ALBUTEROL INHL
ALBUTEROL INHL SOLN
METAPROTERENOL INHL
METAPROTERENOL INHL SOLN

Summary of Pipeline Agents Expected to Offer Related Treatment Options

An NDA for XOPENEX HFA a hydrofluoroalkane (HFA) metered-dose inhaler for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible obstructive airway disease is currently under FDA review (the NDA was accepted for review on July 15, 2004). The Prescription Drug User Fee Act (PDUFA) date for XOPENEX HFA MDI is March 12, 2005.[15]

Class Effects:	Short-Acting Beta-2 Agonists: Oral Inhalation & Nebulized
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Sympathomimetic agents are used to produce bronchodilation. They relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, bronchitis, emphysema, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. The pharmacologic actions of these agents include: alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); $ß_1$-adrenergic stimulation (increased myocardial contractility and conduction); and $ß_2$-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cells and basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; a and ß receptor-mediated lipolysis; a and ß receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic glucogenolysis/gluconeogenesis, and pancreatic beta cell secretion. The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. $ß_2$ selective agents provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity. Note: Levalbuterol is the R(-)-enantiomer of racemic albuterol.
Contraindications	Hypersensitivity, hyperthyroidism, tachycardia or tachycardiac arrhythmias, or aortic stenosis
Major AEs / Warnings	Nervousness, tremor, tachycardia, palpitations, GI upset, nausea. Caution in hyperthyroidism, diabetes, and CV disorders.
Drug Interactions	Atomoxetine: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred).
Special Populations	
Hepatic Impairment	No adjustment necessary.
Renal Impairment	No adjustment necessary.
Pregnancy	Pregnancy Category C.
Geriatric	Dosage reductions required for geriatric patients.
Race	No data

Drug Class:	Short-Acting Beta-2 Agonists: Oral Inhalation			
Characteristic	**albuterol**		**metaproterenol**	**pirbuterol**
	Proventil®	Ventolin®	Alupent®	Maxair® Autohaler
Date of FDA Approval[1]	January 1, 1982	January 1, 1982	January 1, 1982	November 30, 1992
Generic available?[1]	Yes, except for HFA aerosol	Yes, except for HFA aerosol	No	No
Manufacturer[1] (if single source)	Schering	GlaxoSmithKline	Boehringer Ingelheim	3M Pharm.
Dosage forms / route of admin[8-14]	MDI HFA MDI	HFA MDI	MDI	Autohaler (Breath Actuated)
Dosing frequency[8-14]	Use prn for attacks 3-4 times daily or 15 mins before exercise for prophylaxis.		Use 3-4 times daily.	Every 4 to 6 hours.
General dosing guidelines[8-14]	(Adults and children) Relief of bronchospasm, prevention of asthma symptoms: 1 to 2 inhalations every 4 to 6 hours. Prevention of exercise-induced bronchospasm: 2 inhalations 15 minutes before exercising.		(Adults and children) 2 to 3 inhalations no more than once every 3 to 4 hours; to a maximum of 12 inhalations/day.	(Adults and children 12 years) Usually 2 inhalations every 4 to 6 hours. In some, 1 inhalation every 4 to 6 hours may suffice. Maximum of 12 inhalations/day.
Pediatric labeling[8-14]	12 years and up	4 years and up	12 years and up	12 years and up
Other Studied Uses[4]	Treatment of hyperkalemia in patients with renal disease, COPD, cardiogenic shock, Gamstorp's Syndrome. Gamstorp's Syndrome is adynamia episodica hereditaria (hyperkalemic periodic paralysis).		Exercise induced bronchospasm.	Congestive heart failure

Drug Class:	Short-Acting Beta-2 Agonists: Nebulized			
Characteristic	albuterol		levalbuterol	metaproterenol
	AccuNeb	Proventil	Xopenex	Alupent
Date of FDA Approval[1]	April 30, 2001	January 14, 1987	March 25, 1999	June 30, 1983
Generic available?[1]	No	Yes	No	Yes
Manufacturer[1] (if single source)	Dey	Available generically	Sepracor	Available generically
Dosage forms / route of admin[9,10,12]	0.63mg/3ml and 1.25mg/3ml nebulizer solution (Preservative free)	0.083%, 3ml UD vials. 0.5%, 20 ml container with dropper nebulizer solution.	0.31, 0.63, and 1.25mg/3ml nebulizer solution (preservative-free, sulfuric acid, in 3 mL UD vials)	5% nebulizer solution in 10ml and 30 ml container w/dropper - may contain EDTA and benzalkonium chloride. 0.4% and 0.6% solution for nebulization in 2.5ml UD vials, may contain EDTA.
Dosing frequency[4]	Use 3-4 times daily	Use 3-4 times daily	Every 6-8 hours	Use 3-4 times daily
General dosing guidelines[9,10,12]	The usual starting dosage for patients 2 to 12 years of age is 1.25 mg or 0.63 mg administered 3 or 4 times/day, as needed, by nebulization. More frequent administration is not recommended. Deliver over 5 to 15 minutes.	Adults and children 12 years of age: 2.5 mg 3 to 4 times/day by nebulization. Dilute 0.5 mL of the 0.5% solution with 2.5 mL sterile normal saline. Deliver over 5 to 15 minutes. Children 2 to 12 years of age (15 kg): 2.5 mg (1 UD vial) 3 to 4 times/day by nebulization. Children weighing < 15 kg who require <2.5mg/dose (ie, less than a full UD vial) should use the 0.5% inhalation solution. Deliver over 5 to 15 minutes.	(Adults, adolescents 12 years) Start at 0.63mg three times daily by nebulization. May increase to 1.25mg three times daily if needed, tolerated. (Children 6 to 11 years) 0.31mg three times daily by nebulization. Max 0.63mg three times daily.	Usually, treatment does not need to be repeated more often than every 4 hours to relieve acute bronchospasm attacks. In chronic bronchospastic pulmonary diseases, give 3 to 4 times/day. A single dose of nebulized metaproterenol in the treatment of an acute attack of asthma may not completely abort an attack. Not recommended for children < 12 years of age. Administer the unit-dose vial by oral inhalation using an intermittent positive pressure breathing (IPPB) device. The usual adult dose is 1 vial per nebulization treatment. Each 0.4% vial is equivalent to 0.2 mL of the 5% solution diluted to 2.5 mL with normal saline. Each 0.6% vial is equivalent to 0.3 mL of the 5% solution diluted to 2.5 mL with normal

Drug Class:	Short-Acting Beta-2 Agonists: Nebulized			
Characteristic	albuterol		levalbuterol	metaproterenol
	AccuNeb	Proventil	Xopenex	Alupent
				saline.
Pediatric labeling[9,10,12]	2 years and up		6 years and up	12 years and up
Other Studied Uses[4]	Treatment of hyperkalemia in hemodialysis. COPD, cardiogenic shock, Gamstorp's Syndrome. Gamstorp's Syndrome is adynamia episodica hereditaria (hyperkalemic periodic paralysis). A form of periodic paralysis in which the serum potassium level is elevated during attacks; onset occurs in infancy, attacks are frequent but relatively mild, and myotonia is often present; autosomal dominant inheritance.		Exercise induced bronchospasm Hyperkalemia. COPD	

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Abstracts

Levalbuterol nebulizer solution: is it worth five times the cost of albuterol?

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Albuterol is a 50:50 mixture of R-albuterol, the active enantiomer, and S-albuterol, which appears to be inactive in humans. The Food and Drug Administration recently approved levalbuterol, the pure R-isomer, as a preservative-free nebulizer solution.

Published studies indicate that it is neither safer nor more effective than an equimolar dose of racemic albuterol (levalbuterol 1.25 mg = albuterol 2.5 mg). However, these studies were conducted in patients with stable asthma (at the top of the dose-response curve), whereas a nebulized bronchodilator most likely would be used by patients with an acute exacerbation. Because such patients, in the hospital setting, often require higher doses of albuterol, the manufacturer's recommended dose of levalbuterol is likely to be too low for rescue therapy. Levalbuterol may cost as much as 5 times more than racemic albuterol, depending on purchase method.

We conclude that levalbuterol offers no advantage over albuterol but is likely to be more costly.

Levalbuterol and racemic albuterol: Are there therapeutic differences?

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In a 1998 report in the JACI, Nelson et al[1] concluded that levalbuterol (the generic name for R-albuterol administered as a single enantiomer) had a better therapeutic ratio than racemic albuterol (which contains both the R- and S-enantiomers of albuterol). The following year, Gawchik et al[2] likewise concluded that levalbuterol had fewer ß-agonist–mediated side effects than racemic albuterol when administered in doses that produce similar efficacy. Handley et al[3] also reported that nebulized levalbuterol, in doses yielding comparable bronchodilation, had fewer ß-agonist–mediated side effects than nebulized racemic albuterol (R,S-albuterol). All 3 reports implied that levalbuterol had a therapeutic advantage over racemic albuterol because less R-albuterol was required to produce the same degree of efficacy when administered as levalbuterol than when administered in a racemic formulation. Negative effects of the S enantiomer were proposed as the explanation for this. The lower dose of R-albuterol (levalbuterol), in turn, resulted in fewer systemic effects for the same degree of bronchodilator efficacy (ie, a better "therapeutic ratio").

However, in a report appearing in this month's issue of the Journal, Lötvall et al[4] arrived at a different conclusion. They failed to find any difference between the therapeutic ratios for levalbuterol and the racemic formulation. Specifically, they found that all pharmacologic effects of racemic albuterol reside with levalbuterol (the R-enantiomer) and that the S-albuterol was clinically inactive. Why the difference, and which conclusion should guide therapeutic decision-making?

Concerns about potential adverse effects of S-albuterol were first supported by results obtained from preclinical animal and in vitro models.[5] [7] These studies, previously reviewed in the pages of this Journal,[8] [10] indicated that S-albuterol had proinflammatory effects, increased airway smooth muscle responsiveness to LTC4 and histamine, and acted in opposition to the airway protective effects of R-albuterol (levalbuterol) against antigen-induced bronchospasm.

On the basis of these preclinical studies, clinically relevant adverse effects of S-albuterol in human beings were postulated.[10] These included the following: diminution of the efficacy of R,S-albuterol by working in opposition to the bronchodilator and bronchoprotective effects of R-albuterol; the development of tolerance to beneficial effects of R,S-albuterol with repeated use, based on the preferential accumulation of S-albuterol versus R-albuterol in the lung; increased airway responsiveness, possibly due to proinflammatory effects of S-albuterol; and the potential for producing paradoxical bronchospasm. The potential for these clinically important adverse effects from S-albuterol provided the rationale for clinical development of a nebulized formulation of relatively pure R-albuterol (levalbuterol) and its marketing under the trade name Xopenex.

Because the conclusions of Lötvall et al[4] in this issue of the Journal conflict with those in the other publications noted above,[1] [3] it is appropriate to reexamine the weight of evidence from all of the published clinical trials that have attempted to test the hypothesized adverse effects of S-albuterol and the associated potential benefits of using levalbuterol rather than racemic albuterol.

Hypothesis: S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol

If true in human beings, this adverse effect of S-albuterol would cause R-albuterol, administered as levalbuterol, to be significantly more potent than an equal amount of R-albuterol given in the racemic formulation. Let us first look in more detail at the studies whose conclusions supported this hypothesis. The study by Nelson et al evaluated the bronchodilator effects of the levalbuterol and racemic formulations in 362 adolescent and adult subjects treated with levalbuterol, racemic albuterol, or placebo 3 times daily for 4 weeks. Two doses of each formulation were given: 630 and 1250 µg of levalbuterol and 1250 and 2500 µg of the racimate. These doses were matched to deliver the same quantities of R-albuterol (ie, 630 and 1250 µg). The mean peak change in FEV1 from baseline that occurred with the active regimens ranged from approximately 35% to 42%. Given the mean baseline FEV1 of approximately 60% of predicted, this is consistent with postbronchodilator values that differed very little, averaging from approximately 81% to 85% of predicted for each of the active regimens. Although the mean differences between active regimens were small, a statistically significant difference was found between levalbuterol and the racemic preparation after the first dose, though not after 4 weeks of 3-times-a-day treatment.

In a study of 43 children, Gawchik et al[2] compared 4 single doses of levalbuterol, ranging from 160 to 1250 µg, with 1250- and 2500-µg doses of the racemic formulation. Although all regimens provided a significant bronchodilator effect in comparison with placebo, no significant difference in bronchodilator effect could be demonstrated between any of the active regimens.

The report of Handley et al[3] compared several doses of levalbuterol, ranging from 310 to 1250 µg, with a 2500-µg dose of the racemic formulation. No significant differences between active regimens were reported among the 20 adult subjects.

Authors of all 3 of these studies[1] [3] found similar bronchodilatation for the 630-µg dose of levalbuterol and the 2500-µg dose of racemic albuterol. This has been taken to indicate that levalbuterol as the single enantiomer has a better therapeutic index by being more effective and having less potential for adverse effects in the absence of the S-enantiomer.

However, none of these studies provides strong support for the hypothesis that R-albuterol is more potent when administered as levalbuterol than when administered in the racemic formulation. In fact, the results of each of these studies violate the basic validity criteria that apply to investigations intended to compare the potencies of formulations.[12] [13] Such violation occurs in more than one way, but the most important is this: none of these studies was able to demonstrate a significant dose-response relationship. Stated another way: If these studies cannot detect differences between different doses of the same formulation, then they clearly are inadequate to evaluate and quantitate differences between different formulations.

Rigorous methods for comparing and estimating differences in potency of inhaled ß-agonist formulations have been published.[12] [14] [16] These methods use bioassay study design and statistical analyses to estimate differences in potency and are capable of making such estimates with a high degree of precision. The study by Lötvall et al,[4] reported in this issue of the Journal, is the first to use statistical bioassay methodology to estimate the relative potency of levalbuterol and racemic albuterol. The authors examined the results of progressively increasing doses of R- or S-albuterol ranging from 625 to 3200 µg as the individual enantiomers and combined in the racemic formulation. The potency ratio that they calculated for R- versus R,S-albuterol was 1.9, indicating that each microgram of levalbuterol was equivalent to 1.9 µg of racemic albuterol. The 95% CI encompassed a relative potency of 2, as would be expected if all pharmacologic effects of racemic albuterol were entirely from the R-enantiomer. In other words, the pharmacologic activity of the R enantiomer was the same when the single enantiomer (levalbuterol) was used as when the S-enantiomer was also present, as in the racemic formulation. Although this study can be criticized for using a cumulative-dose design, which confounds the effects of time and dosing,[17] the authors' approach nonetheless provides the most reliable estimates of differences in potency between levalbuterol and racemic albuterol available to date.

Several other studies that have tested this hypothesis using albuterol-induced protection against methacholine challenge. Perrin-Fayolle,[18] in a brief report published as a letter in The Lancet, described enhanced protection against methacholine challenge when levalbuterol (identified as D-salbutamol in the report) was administered as the

single enantiomer in comparison with racemic
albuterol and reported that S-salbutamol (identified as L-salbutamol in the report) increased airway sensitivity to methacholine. However, the differences observed between levalbuterol and the racemic formulation were not statistically significant, and others have failed to find any evidence of a difference in bronchoprotective or bronchodilator effect between R-albuterol given alone and R-albuterol given at the equivalent dose in the racemic formulation.[19] [20]

The weight of evidence thus supports neither the concept that S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol nor the concept that there is any difference in R-albuterol potency when it is administered as a single enantiomer rather than in a racemic formulation.

Hypothesis: S-albuterol is responsible for development of tolerance to the beneficial effects of R,S-albuterol

If true in human beings, this would cause the tolerance after repeated administration of levalbuterol to be absent or at least smaller in magnitude than that associated with racemic albuterol. Only a study by Cockcroft et al[21] addresses this hypothesis. They administered R-albuterol alone, S-albuterol alone, racemic albuterol (all enantiomers in equimolar doses), or placebo for 6 days. On days 0 and 7, they evaluated the protective effect of the R-albuterol on methacholine responsiveness. They found a significant and equivalent degree of tolerance after R-albuterol and racemic albuterol treatment but not after S-albuterol or placebo treatment. This does not support the hypothesis that S-albuterol is involved in the induction of tolerance to bronchoprotective effects of albuterol and argues against the suggestion that less tolerance develops when R-albuterol is administered as the single enantiomer (levalbuterol) than when it is administered in a racemic formulation.

Hypothesis: S-albuterol increases airway hyperresponsiveness

If true, this would result in less hyperresponsiveness after administration of levalbuterol than after administration of the racemic formulation. The study by Nelson et al showed that after 4 weeks of treatment there was a small increase in baseline FEV1 with placebo or levalbuterol but not with racemic albuterol. This was statistically significant only in a subgroup of subjects using inhaled corticosteroids. The authors suggested that this might have been due to an increase in airway responsiveness caused by the S-enantiomer.

Four studies have directly tested this hypothesis using bronchoprovocation techniques.[18] [21] The brief report of Perrin-Fayolle[18] indicated a significantly lower PC20 FEV1 to methacholine 3 hours after treatment with S-albuterol in comparison with placebo. However, the other 3 studies failed to find changes in responsiveness to methacholine or adenosine monophosphate from inhalation of single[19] [20] or multiple[21] doses of S-albuterol.

Thus evidence in support of the hypothesis that S-albuterol increases airway hyperresponsiveness is at best inconclusive.

Hypothesis: S-albuterol is responsible for inducing some or all of the paradoxical bronchospasm seen with racemic albuterol

If true, this would result in a lower incidence of paradoxical bronchospasm after treatment with R-albuterol than after treatment with R,S-albuterol. Unfortunately, there are no studies that directly test this hypothetical adverse effect of S-albuterol.

Hypothesis: S-albuterol itself causes some of the systemic effects seen with inhaled albuterol

No authors of published preclinical studies or of papers that reviewed these studies have actually posed this hypothesis. Nonetheless, 2 other groups of authors have addressed this issue in normal volunteers.[22] [23] In addition, the current report by Lötvall et al[4] addresses the issue in subjects with asthma. All of these reports concluded that all observed systemic effects of racemic albuterol are due to the R-enantiomer.

So where are we now regarding a basis for decision-making? Although the preclinical data remain intriguing, available clinical data provide little support for the routine use of levalbuterol over the racemic formulation. Perhaps adverse effects of S-albuterol can be demonstrated in more severely ill asthmatic patients seen in the emergency room or intensive care unit when much larger doses are given for sustained periods. Studies in these clinical settings using appropriate methodology would be of interest.

For now, however, we have to deal with the data at hand concerning the potential benefits and costs of using pure R-albuterol over the traditional racemic formulation. Taken as a whole, the available data provide no evidence that levalbuterol is any safer or more effective than doses of racemic albuterol that contain equimolar doses of R-albuterol. Similar views have been expressed by others.[24] [25] Thus there appears to be no compelling reason to use levalbuterol rather than any other preservative-free albuterol aerosol. Considering the greater cost that is currently associated with Xopenex (Table I), routine use of this product has the potential to increase the cost of asthma care without identified benefit.

Table I. Range of costs per usual dose for different formulations of albuterol aerosol preparations taken from 4 major online-pharmacy Web sites

Product	Price range per dose (US $)
Xopenex (0.63 or 1.25 mg/3 mL)	1.91 - 2.17
Albuterol (2.5 mg/3 mL)	0.80 - 0.88
Albuterol MDI (200 inhalations, 2 inhalations/dose)	0.14 - 0.20

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Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment.

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Cochrane Database Syst Rev. 2003;(2):CD001285.

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BACKGROUND: Inhaled short-acting beta-2 agonists are the major class of bronchodilators used for relief of symptoms in asthma. There has been concern that excessive uncontrolled use of beta-2 agonists might have contributed to rises in asthma mortality seen in some countries. International consensus guidelines now generally recommend using short-acting beta-2 agonists only for relief of symptoms on an as needed basis.

OBJECTIVES: To assess the effects of using short-acting inhaled beta-2 agonists regularly or only on demand in asthmatic adults and children on indices of asthma control.

SEARCH STRATEGY: Searches were carried out of the Cochrane Airways Group "Asthma and Wheez* RCT" register in 1997, 1999 and 2002. Pharmaceutical companies and researchers with an interest in the area were asked directly for details of any studies that they knew of.

SELECTION CRITERIA: Randomised controlled trials
in which the short-acting beta-2 agonist was given regularly in the experimental group, together with an inhaled bronchodilator for relief of symptoms ('rescue use'). The control group consisted of matching placebo inhaled regularly, with an inhaled bronchodilator for 'rescue use'.

DATA COLLECTION AND ANALYSIS: Data were extracted and quality assessments were made by both reviewers. Parallel group and cross-over trials were analysed separately. Where possible data were pooled using a fixed effects model.

MAIN RESULTS: 800 abstracts were identified for the first version and 60 papers were requested for full assessment. In this update 15 studies were added to the 34 trials which met the entry criteria for the first version in 2000. No clinically or statistically significant differences were found in airway calibre measurements. The regular treatment groups required less rescue medication, -0.80 puffs/24 hours (95% CI -0.07 to -1.30) and -0.42 puffs/daytime (95% CI -0.12 to -0.72), and had fewer days with asthma symptoms, -6.7% (95% CI -2.7 to -10.7). There was no significant difference in the odds ratio for the occurrence of at least one major asthma exacerbation either in parallel group or cross over studies.

REVIEWER'S CONCLUSIONS: In general, these results support current guidelines, although it has given reassuring evidence against concerns over regular use of inhaled short-acting beta-2 agonists.

The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients.

Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J.

J Allergy Clin Immunol. 2001 Nov;108(5):726-31.

Supported by GlaxoSmithKline

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BACKGROUND: It has been suggested that R-albuterol produces bronchodilation that is comparable with that of racemic albuterol (RS-albuterol) on a 4:1 dose-for-dose basis but systemic side effects on a 2:1 basis, implying better therapeutic ratio for R-albuterol.

OBJECTIVE: We sought to carefully compare the bronchodilating and systemic effects of R- and RS-albuterol by using a crossover study design.

METHODS: Twenty asthmatic patients (15.1%-28.7% FEV(1) reversibility) were given R-albuterol (6.25-1600 microg), S-albuterol (6.25-1600 microg), RS-albuterol (12.5-3200 microg), or placebo in a crossover, double-blind, placebo-controlled fashion. Cumulative doses were given with a Mefar dosimeter, and FEV(1), heart rate, and plasma K(+) levels were measured 20 minutes after each dose.

RESULTS: Both R- and RS-albuterol produced dose-related improvement in FEV(1) and, at higher doses, increased heart rate and decreased plasma K(+) levels. Neither placebo nor S-albuterol had any significant effect. Individual estimates of the potency ratio for R-albuterol/RS-albuterol were calculated and summarized across all subjects. The geometric mean potency ratio for effects on FEV(1) was 1.9 (95% CI, 1.3-2.8), on HR of 1.9 (95% CI, 1.3-2.9), and on K(+) level of 1.7 (95% CI, 1.3-2.1).

CONCLUSION: All pharmacologic effects of RS-albuterol reside with the R-enantiomer, and S-albuterol is clinically inactive. The R-albuterol/RS-albuterol potency ratios for local (FEV(1)) and systemic effects (heart rate and K(+)) are similar, suggesting a comparable therapeutic ratio for R-albuterol and RS-albuterol in asthmatic subjects.

Drug Class:	Inhaled Long-Acting Beta Agonists	
Drugs Reviewed:	Salmeterol (Serevent Diskus®)	Formoterol (Foradil Aerolizer®)

Class Summary: Indications, Class Effects, and Uniqueness

The purpose of this section is to provide a general overview and comparison of the available drugs within this class. More specific details on the specific drugs available and supporting clinical trials related to this information are presented in subsequent sections.

- There are currently two long-acting inhaled beta agonists available in the United States as indicated above.
- There are currently four FDA approved indications for the two long-acting inhaled beta agonists.
- Salmeterol is available as a DPI and in combination with fluticasone (Advair®); formoterol is only available as a DPI in this country.
- A combination formoterol/budesonide product is available world-wide. While the fixed-dose combination of ß-agonist/steroid offers potential to increase patient compliance and convenience, the ability to individually titrate to the patient's needs is diminished.
- Formoterol has a more rapid onset of action (1-3 minutes) when compared to salmeterol (10 to 20 minutes); however, there is no difference in duration of effect between these agents (8 to 12 hours). This is not considered a very distinguishing feature as the long-acting inhaled beta agonists are used chronically and should not be used as rescue therapy.
- In a pharmacoeconomic and quality-of-life (QOL) study (Rutten-van Molken et al, 1998), formoterol and salmeterol for asthma treatment were found to be comparable. In a randomized study of 482 patients (aged 18 to 78 years) receiving formoterol or salmeterol for 6 months for treatment of asthma, the number of episode-free days and the number of patients reaching clinically-relevant quality-of-life (QOL) improvement was similar in both groups. Total health-care costs, including physician visits, hospitalization, emergency room treatment, medication costs, and non-medical costs were also similar between the two drugs.
- Contraindications, warnings, adverse drug events, and drug interactions are similar for all long-acting inhaled beta agonists and are considered class effects. Refer to *Class Effects* table for more details.
- It was previously suggested that an increased risk of death or near death from asthma may be associated with the regular use of inhaled beta agonists. A subsequent study demonstrated that patients with mild intermittent asthma were neither harmed nor did they benefit from regularly scheduled daily use of short-acting inhaled beta agonists.
- Data from a large, placebo-controlled US study (Salmeterol Multicenter Asthma Research Trial [SMART]) that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in African-American asthma patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) vs. those on placebo (4 of 13,179). Although no difference was noted in the primary endpoint of combined number of respiratory-related deaths and life-threatening experiences, there were differences in the secondary endpoints related to asthma-related deaths and life-threatening experiences. Although the study was not originally designed to assess demographical differences in outcomes, a post hoc subgroup analysis revealed a statistically significantly greater risk in African Americans for both the primary (20 versus 7, respectively) and secondary measures (19 versus 4 for combined number of serious asthma events, and 8 versus 1 for asthma-related deaths). Caucasian patients did not show an increased risk of such events.[6]

Summary of Indications

- Maintenance treatment of asthma and prevention of bronchospasm;
- Nocturnal asthma;
- Exercise Induced Bronchospasm (EIB);
- COPD
-

Place in Therapy

Use of a long-acting beta2-agonist, such as salmeterol and formoterol, is generally recommended in patients with persistent asthma symptoms that require add-on therapy to routine use of inhaled steroids; they may also be helpful in patients with only exercise-induced asthma. They are particularly useful for those patients with asthma who have nocturnal symptoms who are not adequately controlled on inhaled steroids.

Long-acting beta2-agonists are not for acute asthma attacks; inhaled short-acting beta-2 agonists are recommended to be available to all asthma patients for acute asthma symptoms. They are NOT substitutes for inhaled corticosteroids.

Department of Veterans Affairs Formulary

No long-acting inhaled ß-agonists on national formulary

Summary of Pipeline Agents Expected to Offer Related Treatment Options

Pipeline:

Foradil® Certihaler ™ (formoterol fumarate inhalation powder) is a breath-activated multi-dose dry powder inhaler device (MDDPI) device with SKYEPROTECT ™, a powder formulation that protects the drug from atmospheric moisture to ensure product stability and dose-to-dose reproducibility. The dry powder inhalation device contains 60 doses. The FDA has issued an 'approvable' letter for Foradil® Certihaler™.

Arformoterol is a long-acting bronchodilator under development by Sepracor for the maintenance of COPD. Sepracor has initiated or completed 15 clinical studies for arformoterol inhalation solution for the treatment of bronchospasm in patients with COPD. Phase II studies for arformoterol showed a significant improvement in FEV_1 immediately after dosing, as well as a duration of action of up to 24 hours. In 2003, Sepracor completed a 725-patient, 12-week, pivotal Phase III study of arformoterol.[7]

Class Effects:	Inhaled Long-Acting Beta Agonists
This table lists properties of this drug class that are considered to be class effects, i.e., generally all drugs within this class share these properties.	
Pharmacology	Sympathomimetic agents are used to produce bronchodilation. They relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, bronchitis, emphysema, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. The pharmacologic actions of these agents include: Alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); ß$_1$-adrenergic stimulation (increased myocardial contractility and conduction); and ß$_2$-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cells and basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; a and ß receptor-mediated lipolysis; a and ß receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic gylcogenolysis/gluconeogenesis, and pancreatic beta cell secretion. The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. ß$_2$ selective agents provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity.
Contraindications	Hypersensitivity
Major AEs / Warnings	Tremor, tachycardia, headache, sleep disturbance, agitation and tenseness are the most common side effects.
Drug interactions	MAOIs: An increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blocker: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity:Major TCAs: Increased risk of cardiovascular excitation. Severity: Moderate. Diuretics: May add to effects of medications which deplete potassium. Other: Sympathomimetics may lead to deleterious cardiovascular effects.
Special Populations	
Hepatic/Renal Impairment	No adjustment necessary
Pregnancy	Pregnancy Category: C
Geriatric	No dosage adjustment is necessary. The efficacy and safety of patients 65 years of age or older receiving standard doses did not differ from that of younger patients.
Race	A small but significant increase in asthma-related deaths in African-American asthma patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) vs. those on placebo (4 of 13,179) was found in the SMART study. Whether this is a class effect or specific to salmeterol is unknown at this time.

Drug Class:	Inhaled Long-Acting Beta Agonists	
Characteristic	**salmeterol**	**formoterol**
	Serevent Diskus®	Foradil Aerolizer®
Pharmacology [4,8,9]	Salmeterol xinafoate is a long-acting beta-2 adrenoceptor agonist used as an inhalational agent in the treatment of asthma. The drug is an analogue of albuterol, differing by means of a longer lipophilic side chain. The beta-2 selectivity of salmeterol is similar or superior to that of albuterol. Salmeterol's duration of action following inhalation is approximately 12 hours compared to 4 to 6 hours for albuterol. As the plasma half-life of salmeterol is similar to that of albuterol, the longer duration of action is related to other phenomena. Studies have shown that sustained actions of salmeterol are secondary to firm binding of the lipophilic N-side chain to an "exoreceptor site" located close to the beta-2 adrenoceptor, resulting in localization and persistence of effects. An alternative explanation of the extended duration of action of salmeterol has been proposed. This hypothesis states the prolonged duration of salmeterol is determined principally by its physiochemical interactions with membrane lipid bilayers, rather than distinct exosite/exoceptor binding sites in or near the beta-2 receptor.	Formoterol is a long-acting selective beta-2 adrenoceptor agonist. It is formulated as the fumarate salt for inhalation (metered-dose inhaler and dry powder form) and oral use (tablets and syrup). Structurally, formoterol differs from albuterol and terbutaline by virtue of a longer side-chain; it is also unique in that an acylamino group has been substituted on the benzene ring. Bronchodilation, inhalation: 8 to 12 hours.
Date of FDA Approval [1]	February 4, 1994 MDI discontinued in June 2003	February 16, 2001
Generic available? [1]	No	
Manufacturer (if single source)	GlaxoSmithKline	Novartis
Dosage forms / route of admin [8,9]	50 mcg Diskus inhalation powder	12 mcg Gelatin capsules for inhalation *October 22, 2003: the FDA issued an 'approvable' letter for Foradil® Certihaler ™ (formoterol fumarate in a multi-dose dry powder inhaler): dry powder inhalation device contains 60 doses.*

Drug Class:	Inhaled Long-Acting Beta Agonists	
Characteristic	**salmeterol**	**formoterol**
	Serevent Diskus®	Foradil Aerolizer®
Dosing frequency[8,9]	Every 12 hours	Every 12 hours
General dosing guidelines[8,9]	• (Adults and children 4 years) 1 inhalation (50mcg) twice daily (morning and evening, 12 hours apart). • Exercise-induced bronchospasm: 1 inhalation 30 minutes before exercise, not more often than every 12 hours. • COPD: 1 inhalation twice daily (morning and evening, 12 hours apart).	• Maintenance treatment of asthma (Adults and children 5 years): 1 capsule every 12 hours using Aerolizer Inhaler. • Prevention of exercise-induced bronchospasm: (Adults and adolescents 12 years) 1 capsule inhaled 15 minutes before exercise; additional doses should not be used for 12 hours. • Maintenance of COPD: 1 capsule inhaled every 12 hours. Max 24mcg/day.
Pediatric Labeling[8,9]	4 years and up	5 years and up
Other Studied Uses[4]	Cystic Fibrosis High-altitude pulmonary edema	None listed

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8. Product Information: Foradil(R) aerolizer, formoterol fumarate inhalation powder. Schering Corporation, Kenilworth, NJ (PI revised 10/2002) reviewed 5/2003.
9. Product Information: Serevent(R) Diskus(R), salmeterol inhalation powder. GlaxoSmithKline, Research Triangle Park, NC, (PI revised 08/2003) reviewed 08/2003.

Abstracts

Comparative trough effects of formoterol and salmeterol on lymphocyte beta2-adrenoceptor--regulation and bronchodilatation.

Aziz I, McFarlane LC, Lipworth BJ.

Eur J Clin Pharmacol. 1999 Aug;55(6):431-6.

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OBJECTIVES: The primary aim of the present study was to evaluate comparative trough effects of formoterol and salmeterol on beta2-adrenoceptor regulation and bronchodilator response after regular twice-daily treatment, with a secondary aim to evaluate any possible association with beta2-adrenoceptor polymorphism.

METHODS: Sixteen asthmatic subjects, with mean (SD) age 33(9) years, all taking inhaled corticosteroids and with a forced expiratory volume in 1 s (FEV1) of 81(12)% predicted were recruited to take part in a randomised single-blind, three-way cross-over study. The subjects received three treatments each for 1 week, with 1-week washout periods in between: (1) formoterol dry powder, 12 microg twice daily, (2) salmeterol dry powder, 50 microg twice daily, or (3) placebo, twice daily. Spirometry and lymphocyte beta2-adrenoceptor parameters were measured before the first dose and 12 h after the last dose of each treatment, as well as domiciliary peak flow during each treatment.

RESULTS: There were no differences in beta2-adrenoceptor density (Bmax) between the three treatments prior to the first dose; whereas, after the last dose, Bmax was lower with both active treatments than with placebo, but was significant for salmeterol only--a 1.2-fold geometric mean fold difference (95% CI 1- to 1.4-fold), P = 0.04. Compared with placebo, there were n = 9 of 16 subjects with salmeterol and n = 6 of 16 with formoterol who had a greater than 15% fall in Bmax. Post-hoc trend analysis of polymorphism showed that the propensity for downregulation appeared to be related to the occurrence of an allelic substitution of glycine at codon 16-8 of 13 for salmeterol versus 5 of 13 for formoterol with a greater than 15% fall compared with placebo. There were no significant differences between salmeterol and formoterol in terms of mean or individual values for downregulation. There was evidence of persistent bronchodilator activity with both active treatments compared with placebo; this was significant for forced expiratory flow rate between 25% and 75% of vital capacity (FEF25-75)--the mean difference versus salmeterol was 0.39 1/s (95% CI 0.06-0.70), P = 0.02, and versus formoterol was 0.35 1/s (95% CI 0.16-0.53), P = 0.001. These effects were mirrored by significant improvements in morning peak flow rate compared with placebo--mean difference versus salmeterol was 24 1/min (95% CI 7-42), P = 0.01, and versus formoterol was 36 1/min (95% CI 25-48), P < 0.0001.

CONCLUSION: There were no differences between regular treatment with formoterol and salmeterol in their effects on lymphocyte beta2-adrenoceptor regulation at the end of a 12-h dosing interval, with both drugs exhibiting a residual degree of bronchodilator activity at the same time point. Further studies to evaluate receptor regulation and bronchodilator response are required in susceptible patients who have the homozygous glycine-16 polymorphism.

Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma

Rutten-van Molken MP, van Doorslaer EK, Till MD.

Pharmacoeconomics. 1998 Dec;14(6):671-84.

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OBJECTIVE: The aim of this study was to determine the relative economic consequences of treating asthmatics with twice daily dry powder formoterol 12 micrograms as compared with salmeterol 50 micrograms from a societal perspective.

DESIGN AND SETTING: A randomised, 6-month, open-label study including 482 patients with asthma was conducted in Italy, Spain, France, Switzerland, the UK and Sweden. Medical costs included the costs of medications, physician services, emergency room visits, hospital admissions and lung function and other tests. Travel costs and costs of production loss were also calculated. Unit prices were estimated from external sources. To pool the costs of the 6 countries, European currencies were converted to US dollars using 1995 exchange rates. Outcome measures were the number of episode-free days (EFDs) and the number of patients reaching a clinically relevant improvement in quality of life as measured using the St. Georges Respiratory Questionnaire.

MAIN OUTCOME MEASURES AND RESULTS: There were no significant differences between the 2 treatment arms in the frequency of emergency room visits, hospital admissions, use of rescue medication or contacts with general practitioners (GPs), specialists or nurses. Median medical costs over 6 months were $US828 per patient with formoterol and $US850 with salmeterol. This difference was not statistically significant. In both groups, about 60% of all days were episode-free. Average costs per EFD were about $US9 for both treatments. The average cost per patient reaching a clinically relevant improvement in quality of life was between $US1300 and $US1400. Incremental cost-effectiveness ratios were not calculated because both costs and outcomes were not significantly different. Asthma-related absenteeism ranged between 3 days and 6 months per patient in both groups.

CONCLUSIONS: There was no evidence to suggest that either treatment was more cost effective than the other.

Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action.

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Eur Respir J. 1996 Aug;9(8):1684-8.

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We evaluated the profile of the bronchodilatory effect of three inhaled beta2-agonists, 24 microg formoterol, 50 microg salmeterol and 200 microg salbutamol, in patients with stable, moderately severe asthma. Thirty asthmatics (mean+/-SD age 54+/-8 yrs; forced expiratory volume in one second (FEV1) 58+/-12% predicted; reversibility of FEV1 21+/-8% from baseline) participated in a single-centre, double-blind, randomized, single-dose, cross-over study.

FEV1 was obtained in baseline condition and 10, 20, 30, 60 min, and every hour up to 12 h after inhalation of the trial drug. Specific airway conductance (sGaw) was measured at baseline condition and 1, 3, 5, 7, 10, 20, 30, 60 min, and every hour up to 12 h after inhalation.

Formoterol produced a mean increase in sGaw (as % of baseline) of 44% after 1 min, maximal (135%) after 2 h, and 56% after 12 h. The mean increase in FEV1 was maximal (27%) after 2h, and 10% after 12 h. After salmeterol, mean increase in sGaw amounted to 16% after 3 min, maximal (111%) after 2-4 h, and 58% after 12 h. The mean increase in FEV1 was maximally 25% after 3h, being 11% after 12 h. After salbutamol, mean increase in sGaw was 44% after 1 min and maximal (100%) after 30 min. The peak increase in FEV1 was 25%.

We conclude that formoterol (24 microg) and salmeterol (50 microg) had an equal bronchodilatory capacity, which was similar to that of 200 microg salbutamol and lasted for at least 12 h in patients with asthma. However, formoterol had a more rapid onset of action than salmeterol, equal to that of salbutamol.